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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

AUGUST, 1930

ORIGINAL ARTICLES.

STUDIES ON THE CIRCULATION OF THE FEET IN DIABETES MELLITUS WITH AND WITHOUT GANGRENE.

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The purpose of this investigation was to discover whether aid in the diagnosis and prognosis of peripheral vascular disease could be secured by a study of the circulation in the extremities by certain physiologic methods. The observations recorded hereafter do not afford a solution of the problem attacked but represent an attempt to develop the means whereby a solution may be attained in due time.

In order to obtain data on pregangrenous conditions a large number of patients suffering from a disease frequently complicated by gangrene (diabetes mellitus) have been examined and it is hoped that they can be followed for many years, and the incidence of gangrene determined. In the meanwhile it has been found that the response of the skin to histamin together with the physical findings permits an analysis of the conditions of the circulation in the extremities which cannot be obtained by physical examination alone. This communication seeks to present the methods employed in this analysis, to record the findings in many diabetics who do not have trouble with their feet and in a small number with gangrene, and to point out the significance of these findings as judged from the incidence of trouble already present.

As gangrene of the feet in diabetes has been generally attributed

to a decreased blood supply due to arteriosclerosis the investigation commenced with determinations of "bloodflow" through the feet by the calorimeter method of G. N. Stewart.[1] While interesting results were obtained, this method proved too time consuming to permit the accumulation of enough data to provide the desired information.

The observation of Sir Thomas Lewis[2] that the experimental interruption of the circulation to an extremity prevented the normal development of the skin reaction to histamin, and his conception that this reaction is purposive, producing the local changes required to defend the cells from injury, suggested that the reaction of the skin to histamin might be used as a means of roughly estimating the state of the circulation and the resistance to infection of the extremities.[3] This method has proved simple and rapid enough for routine clinical use. Therefore the normal variability of the reaction, the variation caused by change of temperature, by change of position and by administration of certain drugs have been determined. The reaction has been elicited in a control series of over 100 cases which includes normal persons and patients suffering from cardiac disease, arteriosclerosis, hypertension and from many disease conditions never complicated by gangrene of the extremities. Finally, over 100 diabetics have been tested.

The results show that over one-half the diabetics tested have diminished circulatory responses on their feet which persist despite control of the metabolic defects by diet and insulin; in 34 per cent this impairment is marked. Into this latter group fall the great majority of cases with gangrene and with evidence of circulatory impairment.

The response of the skin to histamin together with the physical findings permits the clinical demonstration of conditions of the circulation not easily recognized by other means, namely: the presence or absence of compensation for sclerosis of large arteries, and the presence of abnormal reactions in small vessels without noteworthy involvement of larger arteries. By means of such information the diabetics may be divided into groups according to the type of circulatory disorder; in two of these the incidence of trouble with the feet was 54 per cent and 36 per cent; in the remainder such trouble was almost completely absent. This high incidence in certain groups plainly suggests that patients showing certain types of reaction and certain physical signs have a much larger chance of developing gangrene than the others; a reëxamination of the series at a future date should provide decisive information.

Estimations of the Circulation of the Feet by Stewart's Calorimeter Method. The calorimeter was constructed, the determinations performed, and the results calculated according to Stewart's directions.[1] Most of the estimations were made with the patient in the sitting position. The feet after fifteen minutes immersion in a bath

TABLE I.—A COMPARISON OF THE CLINICAL EXAMINATION OF THE FEET WITH THE CALORIC OUTPUT.

Subject.	Age.	Diagnosis.	Blood pressure mm. Hg.	Caloric output of feet (cal. per min. per 100 cc.).		Boodflow of feet according to Stewart (gm. per min. per 100 cc.).		Clinical examination.
				Right.	Left.	Right.	Left.	
S	30	Normal	125/72	....	19.4	....	4.4 (2)*	Negative.
A	26	Duodenal ulcer	120/72	....	18.7	....	3.9 (1)	Negative.
Wi	65	Diabetes. Auricular fibrillation	140/60	....	16.0	....	3.6 (1)	Heart enlarged, absolutely irregular, arteries moderately sclerotic, feet negative, dorsalis pedis pulses palpable.
M. L.	13	Diabetes	120/70	13.4	16.2	2.6 (1)	3.0 (1)	Heart, vessels and feet negative.
J. W.	43	Diabetes	110/64	....	13.9	....	2.3 (1)	Heart negative, vessels somewhat thickened. Feet negative except for absent dorsalis pedis pulsation.
J. M.	45	Hemochromatosis	110/68	....	8.9	....	1.9 (1)	Very weak, heart and vessels negative, feet negative except for slate-colored skin.
C. H. S.	32	Diabetes	....	....	8.8	....	1.3 (1)	Heart and vessels negative. Dorsalis pedis pulse just palpable, feet otherwise normal.
M. B.	37	Diabetes	115/75	5.6	....	1.2 (1)	....	Heart, vessels and feet negative, Dorsalis pedis pulse strong.
MacN.	26	Diabetes	100/60	9.4	7.4	1.2 (2)	0.7 (2)	Heart, vessels and feet negative.
J. S.	19	Diabetes	122/76	6.0	5.5	0.9 (4)	1.1 (2)	Recovering from acidosis. Heart and vessels negative, feet always cold to touch, otherwise negative, dorsalis pedis pulse strong.
J. H.	42	Diabetes	80/50	4.7	4.2	0.7 (7)	0.6 (7)	Recovering from acidosis. Heart negative, moderate sclerosis of arteries, edema of feet on prolonged standing, none when tested. On allowing feet to hang down they acquired a purplish tinge, the color returning in four seconds after being obliterated by pressure. Dorsalis pedis easily palpable. Feet always cold to touch.
S. G.	35	Gastric ulcer	85/50	3.1	3.6	0.6 (3)	0.9 (3)	Heart and vessels negative, feet become dusky purple when held down, color returns in 15 to 20 seconds after being obliterated by pressure. Right dorsalis pedis pulse easily palpable; left doubtful. Feet cold.

* Number in parenthesis indicates number of determinations made, each on a separate day. In the cases in which more than one determination was made the average caloric output and bloodflow figures have been given.

at about 32° C. were placed in the calorimeter filled with water at the same temperature, the rise of temperature of the water being measured. The foot was then withdrawn, and the loss of heat from the calorimeter to its surroundings determined.

Criticisms of this method have appeared which indicate that the figure for bloodflow given is too small. Harris and Marvin[4] have demonstrated that the temperature of the blood in the hand veins does not fall to that of the water in which the hand is immersed; this is doubtless true of the feet also. Stewart[5] realized this possibility and regarded his method as giving a figure below which the bloodflow could not lie. Therefore the results recorded in Table I have been expressed both as calories given off and as "bloodflow." Since the body temperatures were all within the normal range and the bath temperatures varied only between 30.2° and 31.7° C., the calories given off are to be regarded as a function of the bloodflow. The inclusion of Stewart's "bloodflow" figure permits comparison with other determinations by this method. The relative agreement between the two sets of figures is obvious.

In this investigation the method has been used only to compare the bloodflow through the feet of normals with that of diabetics and to compare the flow in the same patient, before and after control of his metabolic defect. The similarities and the large differences found are significant. The errors in the method pointed out by Sheard[6] are too small to be of significance in this investigation.

Repeated determinations on four normal subjects made by Stewart[7] under conditions similar to our experiments showed results ranging from 2.86 to 7.91 cc. of "bloodflow" per minute per 100 cc. of foot. My determinations on three normal subjects yielded figures of 4.5, 4.4 and 3.9 cc. per minute per 100 cc. of foot.

The patients tested were all in the wards of the University Hospital. Table I summarizes the results obtained, certain data on 3 diabetics and 2 normals mentioned previously[3] have been included in it. Table II gives the results of repeated determinations on 2 diabetics. It is obvious that the majority of the diabetics tested have a caloric output from their feet far under that of normal persons. Discussion of other significant findings will be reserved until the results of the histamin test have been presented.

Estimations of the Circulation of the Feet by the Histamin Reaction. The physiology of the skin reaction to histamin has been elucidated by Sir Thomas Lewis.[8] The technique of eliciting it has been described.[3] The only change has been the addition of 0.5 per cent of chloretone to the 1 to 1000 solutions of histamin acid phosphate (also called ergamin acid phosphate). This acts as a preservative. After keeping such a solution at room temperature for three months the reaction of the skin to it could not be distinguished from that to a fresh solution containing no chloretone.

TABLE II.—CALORIMETRIC DETERMINATIONS ON PATIENTS SUFFERING FROM ACIDOSIS AND AFTER RECOVERY FROM IT.

Patient.	Date, 1925.	Circulation in feet (gm. per min. per 100 cc. of foot).		Urine.		Fasting blood sugar mg. per 100 cc.	Diet P. F. C. gms. per day.	Units of insulin before				Remarks.
		Right.	Left.	Sugar gm. per day.	Diacetic acid.			Breakfast.	Lunch.	Supper.	Midnight.	
J. H.	April 17	0.5	0.7	51.8	+++	330	45–50–31					
Age 42	April 20	0.5	0.3	26.8	+++	....	60–155–76	30	0	10	0	
	April 24	2.0	1.5	2.7	++	395	61–155–75	35	0	15	0	Foot sore.
	April 28	0.3	0.5	0	0	104	56–150–60	35	0	15	10	Soreness gone.
	May 2	0.6	0.3	0	0	....	57–149–61	30	0	10	10	
	May 7	0.5	0.2	0	0	173	88–150–63	20	0	5	10	
J. S.	April 5	0.4	....	+	+++	223	46–67–56	0	30	10	10	
Age 19	April 6	0.4	0.4	23.9	+++	271	52–108–59	30	0	10	10	
	April 7	0.3	1.9	+	++	....	51–78–61	30	0	10	10	
	April 8	2.4	....	+	0	....	62–97–50	30	0	10	10	Left hospital.

The patients were placed flat on their backs with legs extended. Areas of normal skin were cleansed with alcohol and after complete evaporation a drop of the histamin solution was placed on the surface. With a sharp needle the skin was pricked seven times through the drop, the pricks forming a circle about 5 mm. in diameter, the needle going well into the skin but not deep enough to draw blood. Usually one test was placed above the knee, one about 6 inches below the patella, a third 6 inches above the ankle, a fourth on the dorsum of the foot; in special cases other situations were tested. The resulting reactions were roughly sketched at two and a half, five, ten, and fifteen minutes after initiating them. The reactions normally resulting resemble mosquito bites: first a red spot appears, followed and obliterated by a wheal, surrounded by a reddened area (flare) several centimeters in diameter; a sensation of itching accompanies the reaction.

The series of reactions on normal persons and patients with normal circulations[3] has been extended to include over one hundred determinations.

The normal reaction is complete (that is, both wheal and flare present) within five minutes and the reactions on the foot closely resemble those on the leg and thigh, the distal usually appearing a little slower and being a little less well formed than the proximal. Evidence of diminished circulation in the feet consists of delay in appearance and imperfect development of the reaction on the foot, while the reaction above the knee remains normal.

The results recorded hereafter have been classified solely according to the time of appearance of the wheal and flare; that for the wheal being the time at which it could first be palpated. Useful information can be obtained by observing the height and sharpness of margin of the wheal and the intensity of color of the flare and by comparing different reactions along the leg. But as a rule these features vary inversely with the appearance time, so no attempt has been made to record them separately. As the reactions on the legs usually occupied an intermediate position the discussion will be confined to those on the feet and above the knees. For convenience of expression, the normal reaction, complete within five minutes on both foot and knee, will be spoken of as Grade I; a reaction on the foot lacking wheal or flare or both at five minutes but complete within ten minutes, the reaction above the knee being normal, will be referred to as Grade II; a reaction on the foot failing to become complete within ten minutes, that above the knee being normal, will be called Grade III.

Control Observations on Nondiabetic Subjects. Before proceeding to a discussion of the findings in diabetics it is desirable that several physiologic and pathologic factors which modify the velocity of the histamin reactions be considered. Some of these indicate conditions which must be controlled when the test is made, others enter into the interpretation of the results on certain patients.

The Variation in Speed of Whealing Inherent in the Method, and that Caused by Change of Temperature and of Position, by Drugs, and Skin Abnormalities. The appearance of the wheal can be more accurately timed than other parts of the histamin reaction. The variation in velocity of whealing inherent in the technique of eliciting the reaction varies with the condition of the circulation. Thus whealing on the normal forearm takes place in about two minutes and duplicate wheals usually appear within fifteen seconds of each other. On the normal foot, where wheals appear in about three minutes, duplicate reactions may be expected to appear within one minute of each other. On abnormal legs which wheal in about twelve minutes as much as three minutes may separate duplicate determinations.

Variations in ward temperature have made no significant difference in the velocity of whealing. Cooling the feet by sponging with alcohol and allowing evaporation caused a delay of about one minute in 2 cases. Extremes of cold cause profound alteration in the reaction.[9] When the feet are cold delayed reactions should not be accepted as indicating pathological diminution of circulation.

Intense heat reduces or abolishes the reaction,[9] but in 2 patients with gangrene, tested both at ward temperature and after their legs had been warmed in a cabinet, the reactions showed no noteworthy difference.

Change of position causes marked change in velocity of whealing. All subjects must be tested in the horizontal position or the results are not comparable.

The velocity of whealing on the forearm was determined before, during, and after the increase of blood pressure caused by subcutaneous injection of adrenalin (four subjects), and its decrease by inhalation of amyl nitrite (three subjects). The changes found were not significant for this investigation.

If histamin is pricked into an abnormal area of skin the reaction may be abnormal.[10] Scar tissue may give no reaction. In the presence of subcutaneous edema the reactions may still be normal.

The Histamin Reaction in Nondiabetic Arteriosclerosis With and Without Hypertension. Of 11 cases of marked arteriosclerosis with hypertension 8 showed normal reactions to histamin on their feet and legs; in 1 the reaction on both feet was of Grade II; in 2 others the reaction on one foot was of Grade II, the reaction on the other foot being normal. Two cases which exhibited normal histamin reactions when their blood pressure was 205/40 and 190/115, showed neither wheal nor flare after heart failure had caused the blood pressure to fall to 110/70 and 60/50. Another case with normal reactions on admission when the blood pressure was 180/98, exhibited reactions of Grade II on one foot, Grade III on the other when, after three weeks in the hospital without special treatment, his blood pressure had fallen to 130/85. Three months later he was

much stronger, his blood pressure was 180/110 and the histamin reactions had returned to normal.

Of 7 cases of marked arteriosclerosis without hypertension only 2 showed normal reactions on their feet, in 2 the reactions were of Grade II, in 3 the wheal and flare failed to appear on one or both feet. The reactions above the knees were always normal. Two cases of hypertension without sclerosis showed normal reactions.

These results plainly suggest that arteriosclerosis causes diminution of the histamin reaction on the feet and that an increase in systemic blood pressure by compensating for the sclerotic changes in the arteries may restore the response to normal. This must be remembered in evaluating the results on diabetics.

The Histamin Reaction in Heart Disease. Six cases of valvular heart disease without decompensation (rheumatic mitral and aortic valvulitis, and syphilitic aortic valvulitis) showed normal histamin reactions.

Six cases of cardiac decompensation were studied, the test being repeated as their condition changed. When decompensation was slight the tests were within normal limits even though some edema was present. In severe decompensation the reactions on the feet became delayed, those above the knee remaining normal; *in extremis* all reactions lacked both wheal and flare.

A case of paroxysmal tachycardia gave a Grade III reaction on one foot, Grade II on the other when the pulse rate was 144, the blood pressure 93/70; a few days later when the pulse rate was 64 and the blood pressure 100/58, the reactions were normal.

From these results it is evident that cardiac failure may produce change in the histamin reaction by altering the circulation to the feet and this may be a factor in the results on certain diabetics with cardiac complications. But as cardiac disease does not change the reaction until after signs of serious trouble are obvious, the condition of the heart is not to be considered a factor in the results obtained upon the other diabetics.

The Histamin Reactions in Moribund Conditions. Histamin has been pricked into the skin of 5 moribund patients. The reactions were highly abnormal all along the leg, usually neither wheal nor flare developed. Necropsy was performed in 2 cases and no arteriosclerosis was demonstrated. It is evident that abnormality of reaction may be caused by general circulatory collapse in the absence of peripheral vascular disease.

Histamin Reaction in Peripheral Neuritis and After Peripheral Nerve Injury. Immediately after section of a peripheral nerve the skin supplied reacts normally to histamin; after degeneration of the nerve the skin wheals normally but no flare appears.[11] Similarly in 2 cases of peripheral neuritis the skin in the involved areas whealed normally but never flared. In a case of traumatic injury to the brachial plexus the reaction in the involved area lacked a

flare also. In 2 cases of transverse myelitis the histamin reactions above and below the level of disturbed sensation showed no significant difference. Therefore the presence of a good wheal but no flare is evidence of degeneration of certain peripheral nerves supplying the part tested.

The Circulation of the Feet in Diabetes. *Repeated Estimations in the Same Individual.* The histamin reaction has been elicited repeatedly on the same day or on successive days on normal subjects and on stabilized diabetics without noteworthy variation. But marked change in the general condition may be accompanied by corresponding change in the circulation to the feet. Examples of this have been found in certain cases of severe acidosis, during recovery from the incision of a carbuncle, and on the improvement of a concurrent disease (pulmonary tuberculosis). Some cases of severe reduction of the circulation show improvement under treatment without notable change in their diabetic condition. These cases are of sufficient importance to warrant their description in more detail together with cases in which marked change in their general condition was not accompanied by change in the circulation of the feet.

(*a*) *In Acidosis and on Recovery From It.* Five patients were tested during severe acidosis and after recovery from it. All gave evidence of decreased circulation in the feet during the acidosis, after this had been abolished the circulation of some cases returned to normal, in others it remained at its previous low level.

J. S. (Table II) and A. C. (Table III) were known to have had diabetes for one and one and a half years respectively. Neither had any evidence of arteriosclerosis. Recovery from the acidosis was accompanied by great improvement in the circulation to the feet.

On the other hand J. H. (Table II) had advanced arteriosclerosis. Calorimetric determinations were made every few days until the acidosis was under control. The results show that no permanent improvement of the circulation took place. On one day (April 24) soreness developed under a callus on his left foot around which a reddened area appeared. On this day the circulation was greater, but still below normal in both feet. The soreness had disappeared by the time of the next test and the flows fell to their original low level. In patient C. P. (Table III) the histamin reactions show a similar situation. This patient was arteriosclerotic and was in severe acidosis when first tested. A second test made after the acidosis had disappeared showed a worse circulation than the first.

(*b*) *After the Incision of a Carbuncle.* J. J. (Table III), a mild diabetic with slight arteriosclerosis, was tested when in a weakened condition the day after the incision of a large carbuncle on the back of his neck. Marked reduction of the circulation was found. Several days later he had regained his strength and the tests showed considerable improvement in the circulation.

TABLE III.—HISTAMIN REACTIONS ON THE FEET OF PATIENTS DURING AND AFTER CERTAIN DIABETIC COMPLICATIONS. THE REACTIONS ABOVE THE KNEE WERE ALWAYS NORMAL.

Patient.	Date.	Blood pressure.	Arterio-sclerosis.	Foot.	Wheal at 2½, 5, 10, 15 minutes.	Flare at 2½, 5, 10, 15 minutes.	Remarks.
C. P. Age 38	Oct. 3 1929	90/70	Moderate	R	○○++	○○○○	Severe acidosis, stuporous; blood CO_2 30 volumes, per cent.
				L	○○++	○○○○	
	Oct. 10 1929	92/65	....	R	○○○○	○○○○	Acidosis gone.
				L	○○○○	○○○○	
A. C. Age 33	Nov. 7 1928	110/55	None	R	○+++	○○○○	In coma; blood CO_2 11 volumes, per cent.
				L	○○○+	○○○○	
	Nov. 13 1928	85/62	....	R	○+++	○+++	Acidosis better; blood CO_2 41 volumes per cent.
				L	○+++	○+++	
J. J. Age 57	April 22 1929	135/75	Slight	R	○○○○	○○○○	Carbuncle on back of neck incised April 21. Weak.
				L	○○○○	○○○○	
	April 25 1929	135/85	....	R	○○++	○○○○	Feeling better; stronger.
				L	○○++	○○○○	
N. S. Age 18	May 10 1928	100/62	None	R	○○++	○○++	Active pul. tuberculosis; fever at night.
				L	○○++	○○++	
	Oct. 10 1928	118/75	....	R	○+++	++++	Afebrile; has gained 40 pounds in weight.
				L	○+++	++++	

(*c*) *In Complicating Pulmonary Tuberculosis.* In 2 cases (A. B. and N. S., Table III) the diabetes was complicated by active pulmonary tuberculosis. Both were very weak and the tests showed slight reduction of the circulation in the feet. Some months later, after the tuberculosis had become inactive and they had gained weight and strength, the circulation returned to normal.

(*d*) *In Gangrene.* As most of the cases of gangrene were promptly operated upon, the opportunity to follow their circulation over long periods of time was infrequent. Two cases (P. K. and L. B., Figs. 3 and 4) have been secured. The improvement in the response to histamin coincident with recovery from gangrene is evident.

From these results it is obvious that the circulation of the feet may change considerably *pari passu* with fluctuations in pathologic conditions affecting the general or local circulation. But since rapid changes of significant magnitude do not occur if the diabetes is under control, it seemed of interest to determine the state of the circulation in the feet in a series of 100 consecutive cases whose condition had been stabilized by supervision in the wards and outpatient department of the University Hospital. A few cases previously referred to[3] have been included in this series.

The Response to Histamin on the Lower Extremities of 100 Stabilized Diabetics. The cases have been divided into three groups according to the response to histamin. In 32 cases the histamin reaction indicated a normal circulation in both feet (Group I). In 34 the reaction was of Grade II in one or both legs, indicating slight

diminution of the circulation (Group II). In 34 cases the reaction was of Grade III on one or both feet indicating marked diminution of the circulation (Group III). The almost equal size of the groups is accidental.

In Table IV the statistical data of certain clinical features of these groups are set forth. In Group I only 1 patient has had trouble with the feet: M. T. had ulceration following a burn which healed in a month. The tests were made over a year later. The dorsalis pedis pulse was present throughout the group and only 5 patients exhibited evidence of sclerosis of the peripheral arteries. Three of these had marked hypertension. Group II obviously occupies the intermediate position. One case had serious trouble with the feet at the time of testing and is reported in detail in Fig. 2. No others had any trouble with their feet nor history of it. The average blood pressure is lower than in Group I and this is perhaps a factor in the reduced circulation to the feet. Judging from the number of cases on insulin the diabetes is more severe than in the other group; on the other hand the high average carbohydrate in the prescribed diet is caused by a number of mild cases who were doing well with but little restriction of carbohydrates.

The patients of Group III are older, have had diabetes longer, and have more evidence of arteriosclerosis than the others. In this group occur the great majority of instances of serious trouble with the feet: 5 patients had gangrene at the time of testing; 2 had had gangrene several years previously but had recovered without amputation; 2 more had had their other leg amputated for gangrene; and 2 more had indolent ulcers when tested.

These results suggest that the patient with a markedly delayed or incomplete histamin reaction on his feet has a much larger chance of serious trouble with his feet than when the reaction is more normal. But before the prognostic value of the test can be discussed it is desirable to make a more detailed analysis of the series.

A consideration of the reaction of the skin of the dorsum of the feet to histamin, of the condition of the principal artery supplying the area tested, and of the evidence of generalized arteriosclerosis makes it possible to analyze further the vascular conditions in the feet of any patient. Thus evidence can be secured that compensation for a sclerosis of the supplying vessels has occurred, the reaction of the minute vessels being normal. On the other hand evidence of disease in the minute vessels may be obtained when there is no demonstrable change in the larger. Also in some cases evidence is found that the local vasomotor reflexes do not function though the circulation may be but little reduced.

Therefore it is of interest to arrange the 100 diabetics according to the amount of general arteriosclerosis, the condition of the dorsalis pedis, and the histamin reaction on the dorsum of the foot; and to study the cases composing the different groups in order to throw

TABLE IV.—COMPARISON OF CONDITION OF CIRCULATION TO THE FEET WITH OTHER DATA IN 100 STABILIZED DIABETICS.

	Number in group.	Average age.	Average blood pressure, mm. Hg.	Number of cases with dorsalis pedis pulse of strength given.			Number of cases with sclerosis of peripheral arteries of degree given.			Average known duration of diabetes in years.	Number of cases receiving insulin.	Average insulin dosage of cases on it in units per day.	Average carbohydrate of prescribed diet in grams per day.	Number of cases with gangrene or persistent infections of feet, or history of such trouble.
				Normal.	Weak.	Absent.	Slight.	Moderate	Marked.					
Group I. Normal circulation. Histamin reactions, Grade I	32	44	137/80	30	2	0	3	2	0	4.9	8	28	88	0
Group II. Slight diminution of circulation. Histamin reactions, Grade II	34	44	128/74	25	4	5	4	2	2	4.1	21	32	102	1
Group III. Marked diminution of circulation. Histamin reactions, Grade III	34	55	143/74	18	2	14	8	3	4	6.0	15	38	92	10

light on the clinical value of this new type of evidence. Therefore, the 100 cases have been divided into nine groups, containing the combinations of findings encountered; and a tenth group set apart for special study.

In judging the degree of general arteriosclerosis chief reliance was placed on the condition of the palpable peripheral arteries. In the ward cases additional evidence was secured by observing the retinal arteries and by demonstrating arterial calcification by Roentgen ray.

1. *No Demonstrated Arteriosclerosis—Dorsalis Pedis Pulse Strong.* (1*a*) *Histamin Reactions Normal.* This is the normal situation. Twenty-five cases fall into it. The average age is forty-two, the oldest sixty-nine years. The average duration of diabetes is five years. Only 3 are receiving insulin, so that the majority are mild diabetics. No one has had trouble with the feet. One aged fifty-nine years has a blood pressure of 165/100.

(1*b*) *Histamin Reactions Slightly Delayed* (*Grade II*). This may be thought of as indicating slight pathologic change in the minute vessels but the change in the histamin reaction is but little beyond the limit of technical error. Of the seventeen cases in this group 11 are receiving insulin, so the diabetes is more severe than in the preceding group. None has had trouble with the feet. Two cases have blood pressure of 170/90 and 175/85.

(1*c*) *Histamin Reactions Markedly Delayed* (*Grade III*). This combination provides evidence of change in the minute vessels of the feet without conspicuous lesions of the larger arteries. But the change, whatever its nature, extends up the leg a variable distance but cannot be demonstrated above the knee, the histamin reactions there being normal. A similar situation is sometimes found in certain decompensated cardiacs, but there is nothing to make one suspect the heart in these diabetics. There may be more sclerosis of larger arteries present than was detected by the usual examinations, but there can be no doubt about the presence of a good dorsalis pedis pulse.

In 1 case (M. B.) both the histamin tests and calorimetric determinations (Table I) were made; the low caloric output found indicates that a real diminution of bloodflow must have taken place. In another stabilized diabetic (MacM., Table I) no histamin reactions were elicited, but the low caloric output of his feet and the absence of evidence of sclerosis places him in this group.

No certain interpretation of these findings can be made. The underlying cause may be a functional constriction of arterioles, or sclerotic changes involving primarily the small arteries, or unrecognized cardiac weakness.

Eight cases are found in the group, their average age is forty-eight and they have had diabetes an average of 6.1 years. Four are taking insulin, 3 of these are on large doses, over 40 units per

day. None have hypertension, none have had trouble with their feet. The later history of this group will be followed with much interest.

2. *Generalized Arteriosclerosis Without Obliteration of Dorsalis Pedis Pulse.* (2*a*) *Histamin Reactions Normal.* This indicates that compensatory processes have overcome difficulties caused by the sclerotic changes. Five cases fall into this group. Four have blood pressures of 210/85, 210/85, 180/100 and 152/82 mm. of Hg., the last with but slight sclerosis has a blood pressure of 125/75. The relation of the hypertension to the compensation is evident. No case had trouble with the feet.

(2*b*) *Histamin Reactions Grade II.* Here compensation is not quite complete. Nine cases fall into this group, 2 had slight hypertensions (166/84 and 162/88). One of these had gangrene; the reactions are shown in Fig. 2 and a detailed history is appended. This case had the best histamin reactions of any case of gangrene tested and the lesion was doing well when she died suddenly, apparently from embolism from a complicating phlebitis.

(2*c*) *Histamin Reaction Grade III.* In these cases a marked failure of compensation is indicated, the chief lesion being located distal to the place where the arteries can be palpated. There are 11 cases in this group, 5 had hypertension of over 160 mm. Hg. Two cases (P. K. and L. B.) had gangrene at the time of testing; their reactions are shown in Figs. 2 and 3. Both recovered without amputation. Two others had had gangrene two or three years before, one recovered without amputation, the other had a toe amputated and the foot looks well at present. The ability of the patients of this group to recover from gangrene is striking. The feet of the remainder had no acute lesions.

3. *Generalized Vascular Sclerosis, Obliteration of Dorsalis Pedis Pulse.* (3*a*) *Histamin Reactions Normal.* This would indicate complete compensation. No case completely filling these requirements occurs in the series. Two approach it, in one the dorsalis pedis pulse was recorded as doubtful, in the other it was just palpable. Neither had hypertension. The feet of these patients were in good condition. The development of new vascular pathways is the probable method of compensation.

(3*b*) *Histamin Reactions Grade II.* This indicates partial compensation. Nine cases present these findings; none had hypertension nor trouble with their feet.

(3*c*) *Histamin Reactions Grade III.* This indicates a marked failure of compensation and the clinical data supports this conception. Of the 13 patients in this group over one-half have or have had serious trouble with their feet. Three of these had gangrene when they were tested, 2 came to amputation, the other refused and soon died. Two cases had suffered amputation of the other leg for gangrene. Two patients had indolent infections at the time

of the examination. In 2 cases blood pressures of 230/80 and 260/95 were insufficient to compensate for the vascular lesions. That all the members of this group are in a hazardous situation seems an obvious conclusion. The reactions in 2 cases are shown in Figs. 1 and 5.

4. *Cases with the Histamin Reaction Consisting of a Good Wheal but No Flare.* The 13 cases gathered together under this heading have been included in the preceding groups but deserve special attention. This type of reaction is characteristic of degeneration of peripheral nerves.[11] However I have seen it in a moribund cardiac case who previously had given normal reactions and again in a comatose diabetic (A. C., Table III) who gave normal reactions after the acidosis had been overcome. The cause of disappearance of the local vasomotor reflexes in these cases is not clear.

It must be remembered that when the lack of adequate circulation abolishes both wheal and flare the histamin reaction throws no light on the condition of the peripheral vasomotor reflexes, for they may be present without being demonstrable. No certain division can be made between cases failing to exhibit a flare because of diminished circulation and those in whom its appearance is prevented by degeneration of peripheral nerves; and both conditions may occur together. But when the wheal always appears promptly and becomes well developed and no flare follows, degeneration of the peripheral nerves should certainly be suspected, and it is of interest to examine certain clinical characteristics of the group of diabetics showing this type of reaction.

In 2 cases the wheal appeared within five minutes but no flare followed. In 11 cases the wheal was absent at five but appeared within ten minutes and became well developed, suggesting a disappearance of the reflex together with some diminution of the circulation. Five of the 13 exhibited numbness and paresthesias which led to the clinical diagnosis of peripheral neuritis by the physician in charge, in the remainder this condition was not suspected. A surprisingly large percentage have had trouble with their feet, 3 had gangrene at the time of testing (J. K., Fig. 5 and P. K., Fig. 3 are in this group). Another (L. B., Fig. 4) exhibited this type of reaction after recovery from gangrene, another had previously suffered amputation of the other leg. The group as a whole suggests that a lack of vasomotor response may be a factor in the development of gangrene which deserves more attention. The lack of resistance to infection seen in other nervous diseases is perhaps analogous.

Histamin Reactions on Patients with Gangrene of the Feet. The reactions have been elicited in 14 patients with gangrene of the feet; in 2 the lesions were bilateral. Eight of these patients were seen after the series of 100 cases had been completed. Twelve had diabetes, the remainder were diagnosed arteriosclerosis. The findings

on 5 of the diabetics are pictured in the figures. In all cases the diabetes was easily controlled and the urine and blood sugar became normal within a few days after admission. The legs were placed in a cabinet or bed tent warmed by electric light bulbs, the lesions were lightly dressed.

EXPLANATION OF FIGURES.

The histamin reactions are indicated diagrammatically, and are in scale with the ruled centimeter in the upper left-hand corner. The tests were placed on the anterior aspect of the leg at the level indicated by the relation to the leg diagram. The number indicates the time in minutes after the introduction of histamin. Small dotted circles indicate red spots, the much larger dotted circles indicate the outline of flares. (No attempt has been made to indicate the speckled appearance of some flares.) Wheals are outlined by a solid line, the number of cross hatches indicating height.

The presence or absence of arterial pulsation is indicated by a + or − sign located at the level of the artery on the leg diagram. The letter *P* indicates pain not associated with movement; *C* indicates pain associated with movement (intermittent claudication); *S* indicates disturbance of sensation; these letters are located near the spot where the sensation was felt. Areas of gangrene or of acute inflammation have been shaded.

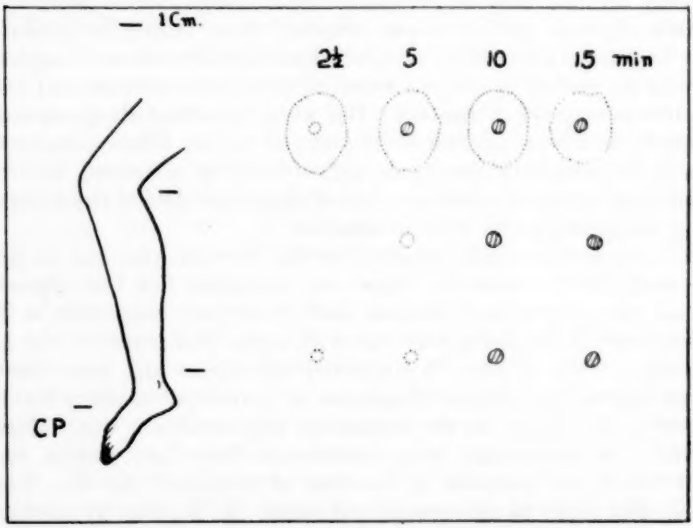

FIG. 1.—J. H., aged fifty-nine years. Diabetes mellitus just diagnosed, foot painful for four months. Foot becomes blue when in dependent position, blanched when elevated. A red flush extended half way over the dorsum, histamin was pricked into this but no response could be seen. Moderate generalized arteriosclerosis. Roentgen ray showed calcification in the arteries of both legs. Auricular fibrillation. Blood pressure 230–130/80. Gangrene of tip of second toe seven days after the tests. Amputation at junction of middle and lower thirds of thigh. Healing of stump satisfactory. Patient died suddenly six weeks after discharge from hospital. No necropsy.

The histamin reactions pictured in Fig. 1 represent the most common finding except that on the dorsum of the foot a red spot is usually seen. Normal reactions occurring only above the knee

occurred in twelve of the sixteen legs with gangrene of the feet. This finding suggests a reason for the surgical experience that amputation below the knee is usually unsuccessful.

The other types of reaction found are illustrated in Figs. 2 to 5. They will be discussed later.

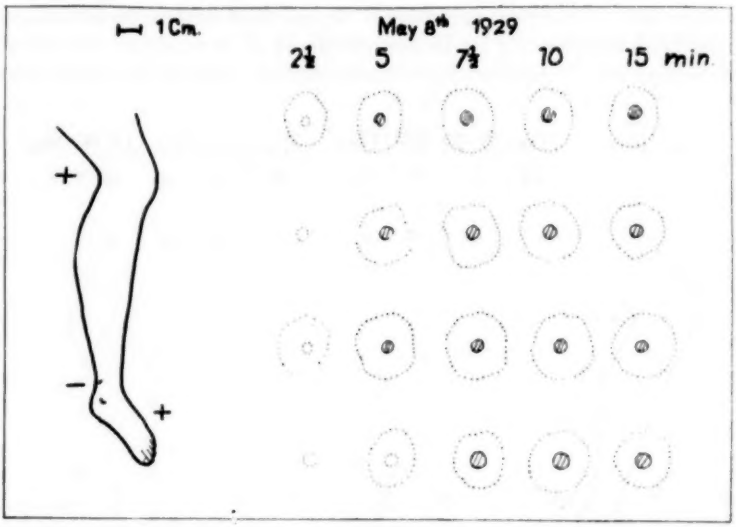

FIG. 2.—E. A., aged forty-one years. Diabetes mellitus for fourteen years. Ulcer under ball of foot for three months, gangrenous spot developed a week before admission with red streaks extending up leg. Slight arterial calcification by Roentgen ray. Foot did well until three days after testing when pain developed in calf, later in popliteal space. Sudden collapse and death two days later. Necropsy not permitted.

Discussion. When histamin reactions are elicited on the feet in the manner prescribed the causes of diminished vascular response can be grouped under two principal headings. First, that due to peripheral vascular disease and characterized by normal responses on the thigh becoming progressively more abnormal down the leg. A second type is to be attributed to cardiac weakness and its accompanying vasoconstriction; in extreme cases it is characterized by abnormal reactions all along the leg, when the condition is less marked by reactions much similar to those seen in peripheral vascular disease. Patients moribund from a variety of causes have shown this type. However, as many cases of mild cardiac decompensation show normal reactions, the cardiac type of reduced reactions is to be expected only when the clinical picture is obvious.

Both of these types may occur together. In patients with peripheral vascular disease marked rapid fluctuations in the general condition have been accompanied by corresponding changes in the

reactions on the feet. Such observations provide evidence that the circulation in the extremities may be increased by an improvement in the patient's general condition; they illustrate a principle underlying the conservative treatment of pedal lesions.

Both the histamin reaction and the studies of caloric output indicate that the majority of diabetics have a subnormal circulation in their feet. Morrison and Bogen[12] found that arterial calcification could be demonstrated by Roentgen ray in 53 per cent of 324 unselected diabetics. At necropsy arteriosclerosis is found in 79 per cent

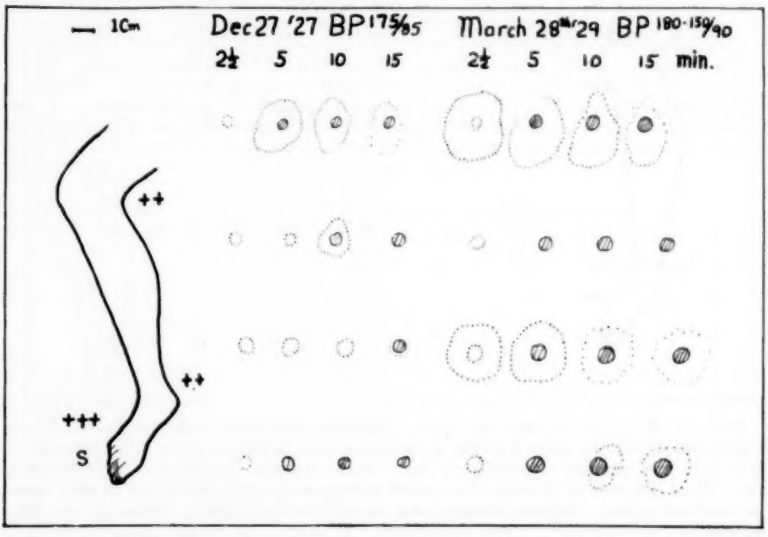

FIG. 3.—P. K., aged sixty-five years. Diabetes mellitus for eighteen years. Sore toe since 1925. Admitted November 26, 1927. First and second toes reddened, swollen, insensitive, pus exudes from below a callus. Bullæ on great toes. Roentgen ray showed loss of substance of terminal phalanx of right great toe with rarefaction of all bones of feet, also considerable calcification in vessels of feet and legs. Very marked arteriosclerosis of all palpable vessels. Paroxysmal auricular tachycardia with slight cardiac decompensation. Discharged February 22, 1928. Readmitted March, 1929. Auricular fibrillation. Lesions of foot healed, only some redness of toes remaining.

of the diabetics in Joslin's series.[13] A case of diabetes and one of arteriosclerotic gangrene tested by Stewart[14] gave a low caloric output in both the gangrenous and the normal foot. Therefore, our results are consistent with other knowledge on the subject and are a demonstration of the feeble cutaneous circulation in diabetes long recognized by clinicians.

Taking the results as a whole there is general correspondence between the clinical examination of the feet and the reaction of the skin of the feet to histamin. The same general agreement is seen between the physical findings and the caloric output (Table I).

Therefore in many cases these tests provide only confirmatory evidence of a normal or pathologic condition of the circulation in the feet. But the results recorded in Table I indicate that a considerable reduction in the circulation may occur without the development of any physical signs and that their full development occurs only when reduction is extreme.

But as soon as individual patients are studied it is seen that the histamin reaction will at times detect change in the circulatory responses when they would not otherwise be suspected, and will demonstrate normal conditions in the minute vessels when the

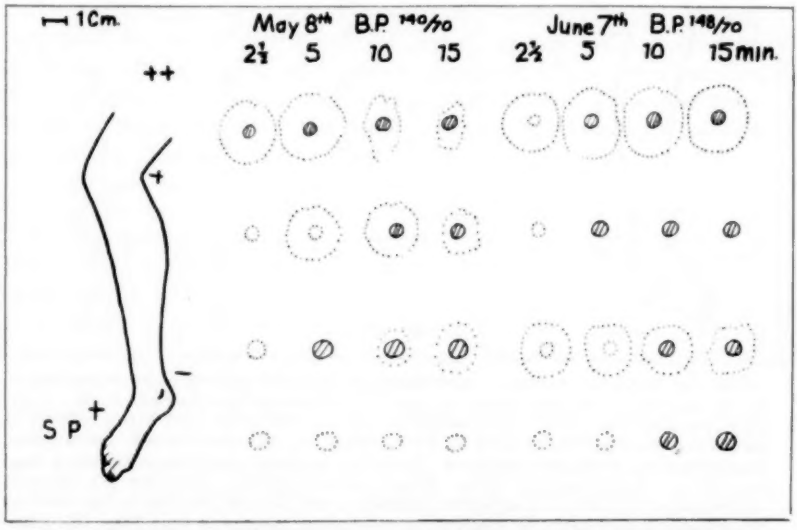

FIG. 4.—L. B., aged fifty-seven years. Diabetes mellitus for fourteen years. Toes sore for six weeks. On admission April 29, 1929 gangrenous ulcer on middle toe surrounded by inflamed area. Great toe also inflamed. Numbness and paresthesias of entire foot. Slight edema to ankle, Roentgen ray showed marked absorption of terminal phalanx of middle toe, and some calcification of dorsalis pedis arteries. Toes healed by May 30, 1929. Paresthesias remained.

physical examination indicates arterial disease. The calorimetric studies also show these two types. Therefore the histamin reaction together with the physical examination permits the easy clinical demonstration of certain conditions long recognized in the pathologic literature, but not associated with individual patients nor made the basis for prognosis and treatment. Thus, it is easy to determine whether the compensatory changes, as rise in general blood pressure and development of new blood paths, have overcome the handicap of a sclerotic main artery. In other cases evidence of abnormal vascular responses without demonstrable sclerosis of larger vessels suggests pathologic change beginning peripherally, and arterio-

sclerosis of this type is not uncommon.[15] In some cases evidence of failure of local vasomotor reflex responses may be secured. Thus the histamin reaction supplements the physical examination, the former demonstrating the physiologic conditions in the minute vessels, the latter providing information concerning the larger arteries.

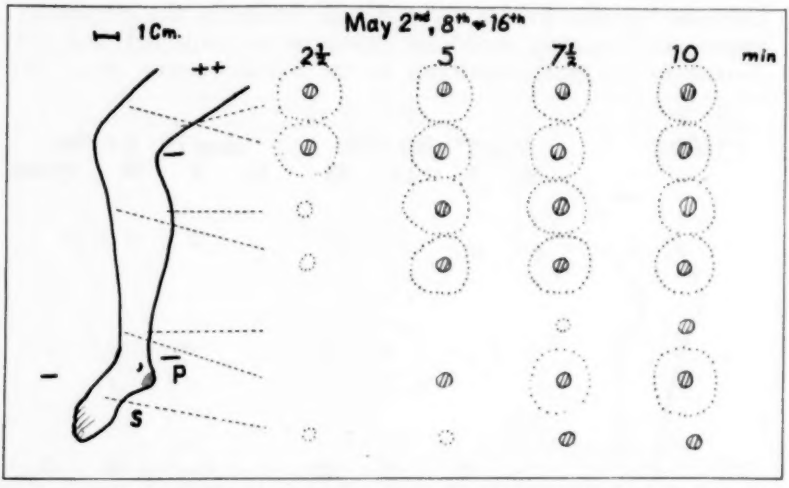

FIG. 5.—Histamin reactions on anterior and posterior aspects of leg as indicated by dotted lines. J. K., aged sixty-six years. Diabetes mellitus for eight years. Heel sore for about three weeks. On admission April 30, 1929, large ulcer with gangrenous margins extending down to os calcis, lower part of leg somewhat wasted, paresthesias over right foot. Râles at lung bases. Retention of urine, blood-urea nitrogen 31 mg. per 100 cc. Slight evening fever. Blood pressure 130/57. Roentgen ray showed tuberculous infiltration of both apices probably active, also calcification in leg arteries. No tubercle bacilli found in sputum. Conservative treatment until May 18, 1929, caused improvement in râles, normal blood-urea nitrogen, slightly less fever; pain persisted, no improvement in gangrene, nor change in histamin reactions.

Amputation May 18, 1929, 8 inches below tibial tubercle. Convalescence stormy, healing of stump delayed. Discharged June 17, 1929, with stump almost healed. July 7, 1929, stump reported healed, August 23, 1929, reported to be getting about on peg leg. January 3, 1930, working, getting about on peg leg, there is an area the size of a match head on stump which is dressed daily; not under care of physician.

Pathologic report on vessels of stump. Grossly anterior tibial essentially normal lumen open, wall possibly a little thick. Posterior tibial small and thickened and a lumen was demonstrated only in the upper portion. Sections confirmatory. Diagnosis endarteritis obliterans of posterior tibial.

It is obvious that data on the 100 diabetics have not been in existence long enough to determine finally their prognostic significance; but several features should be pointed out. The group of cases showing generalized arteriosclerosis with obliteration of dorsalis pedis pulsation and a Grade III histamin reaction contains over 50 per cent of cases with serious trouble with their feet; the situation of patients showing these findings must be regarded as hazardous. The group of cases with generalized arteriosclerosis, a Grade III

histamin reaction, but with a palpable dorsalis pedis pulse also shows a high percentage of trouble, but the number of recoveries without amputation is striking. In contrast to these, the cases with normal histamin reactions show almost complete freedom from trouble with their feet and it would appear that these cases had little to fear from this complication. Attempts at making a prognosis for patients in the intermediate groups had best be suspended until more time has elapsed. The results show one thing clearly, a consideration of both the physical examination and the histamin reaction gives far better indication of the incidence of trouble with the feet than does a consideration of either alone.

In considering the group of cases in which gangrene has already occurred one finds that this condition is usually accompanied by profound alterations in all histamin reactions below the knee, but that gangrene may occur with but little reduction in the reactions. Cases of gangrene when the usual signs of diminished circulation are absent have been reported by others.[16]

In considering the usefulness of the histamin reaction in determining the course of treatment several facts should be pointed out. The histamin reaction can be improved by treatment. A Grade III reaction in a patient with gangrene of the foot does not demand amputation, both gangrene and reaction may improve together.

However a study of the series leaves one with certain definite impressions. Patients with a Grade III histamin reaction on the foot and a good dorsalis pedis pulse have often recovered from gangrene without amputation; in those with similar reactions but with no pulsation in the dorsalis pedis conservative treatment has not been successful. Patients with no complete histamin reactions below the knee have usually come to high amputation or died. Improvement in the reactions after a period of conservative treatment is encouraging, lack of it discouraging. The prognostic significance of the disappearance of the vasomotor reflexes cannot be evaluated from the data now at hand.

In discussing the value of the histamin reactions in choosing the level of amputation certain considerations must be emphasized. A blood supply which perfectly suffices for the nutrition of a limb may be insufficient to ensure cicatrization of a stump.[17] The process of healing is to be thought of as demanding hypertrophy and hyperplasia of the vascular bed with an increased blood supply. Therefore the decision regarding level of amputation should be based not only on the circulatory conditions present before amputation but also upon an estimate of the possibility of increase of circulation. While no criteria exist on which this estimation can be based with certainty, the age and strength of the patient, the duration of the disease, the condition of the heart, vessels, and blood pressure are to be thought of as factors, as well as local vascular conditions.

An abnormal histamin reaction indicating imperfect compensa-

tion would seem to offer a poor chance of successful healing of a stump at that level; no amputation has been advised where the reactions were abnormal. On the other hand normal conditions in minute vessels may have been attained by a maximum of circulatory compensation, and the increase necessary to heal a stump may not be possible. However, as many elderly patients never walk after amputations above the knee and as lower amputations are at times successful, it seems legitimate to attempt this procedure where the histamin reaction is normal, the condition of the large arteries satisfactory, and the general condition good. An amputation below the knee was performed on one of our cases of diabetic gangrene which partly met these conditions and while healing was delayed, a stump was eventually secured which has been supporting an artificial leg for six months. To summarize, an abnormal histamin reaction appears to us to contraindicate amputation at that level, but a normal reaction is no guarantee of success. That this conclusion is based on reasoning rather than on the data must be emphasized; data on this point will accumulate but slowly.

Summary and Conclusions. In a series of 100 unselected diabetics under treatment the response of the skin of the lower extremities to histamin under standard conditions indicated that 32 per cent had a normal circulation in their feet, in 34 per cent the circulation was somewhat impaired, in 34 per cent markedly impaired. The caloric output of the feet was determined thirty times in 8 diabetics; it was constantly below normal in 6 patients. It is concluded that the majority of diabetics have an abnormally low bloodflow through their feet.

The circulation in the feet of certain diabetics may vary markedly with their general condition, but in certain arteriosclerotic diabetics improvement in general condition is not followed by improvement in circulation to the feet. In certain arteriosclerotic individuals the height of the general blood pressure has a marked influence on the circulation to the feet.

The reaction of the skin of the feet to histamin together with the physical findings permits the demonstration of the presence or absence of adaptations to compensate for sclerotic narrowing of the large arteries, and allows the clinical detection of pathologic change in the minute vessels when the larger arteries are not notably involved. In certain cases the presence or absence of local vasomotor reflex responses can be demonstrated.

Such demonstrations permit the assignment of individual cases to one of a number of groups. The great majority of patients with trouble with their feet or history of it fall into two groups characterized by markedly abnormal histamin reactions and generalized arteriosclerotic changes. The data plainly imply that by considering the histamin reaction together with the physical findings a more accurate prognosis can be made than by considering either separately.

The types of histamin reaction occurring on the legs of 14 patients with gangrene of the feet are described. The value of this evidence in aiding the selection of treatment and choosing the level of amputation is discussed.

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NORMAL URINE SUGAR IN CYSTOSCOPIC EXAMINATIONS.

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The presence of a reducing substance in normal urine has been recognized since Pavy, in 1899, held that the kidneys were permeable to small traces of what he thought to be dextrose. Its character and origin, however, are still a matter of discussion. Folin and Berglund[1] and Eagle[2] believe that it is made up of carbohydrates, not dextrose, which are taken in with the food, and which the body is unable to utilize. Greenwald, Gross and Samet[3] give it a double origin; according to Folin, partly from the metabolization of pro-

tein, and, more recently, possibly from carbohydrates formed by intestinal bacteria. Benedict,[4] on the other hand, thinks that it is partly dextrose which has escaped through the kidneys in small amounts from a normal blood sugar. The presence and amount of this substance in the blood are still undetermined, due to inclusion of it, if present, in the regular quantitative methods for blood sugar. Hubbard and Allison[5] have recently pointed out that, if the blood filtrate according to Folin and Wu be fermented with B. coli, and the reduction then determined, there is found a small residue of non-fermentable material which may have some connection with this reducing substance in the urine. In this work we shall speak of this reducing substance as sugar, as it appears that some of it, at least, is carbohydrate.

We have been interested in this sugar from a different angle; namely, the ability of the kidneys to excrete it in health and disease. We wish to report at this time on the results of sugar determinations on urines procured from both kidneys by ureteral catheterization done during cystoscopic examinations. These examinations were made in the course of studying patients who presented symptoms pointing to a lesion in one or the other kidney. The specimens were collected in the customary manner and were sent to the laboratory for routine examination, and culture and guinea-pig inoculation. We have used paired specimens because, as we felt that there was still too much uncertainty regarding this sugar in the blood, it seemed that a comparison of urines from a normal and a damaged kidney, both excreting from the same blood, would make possible a more definite study.

The method used for determining the urine sugar was that of Folin[6] with more recent changes.[7] This method calls for 5 cc. of urine, but on account of the small amount of urine sometimes procured in ureteral catheterization, we have adapted the method for smaller amounts. These examinations were sufficiently checked with those done on the full 5 cc. so that there is no question of their accuracy; the difference in results between the two methods was so small as to be negligible. The results are expressed in mg. per 100 cc. of urine.

It is probable that the blood reaching both kidneys is similar in composition, so that with equal function similar urines should result. In the various forms of nephritis, both kidneys are usually more or less equally affected. In the kidneys presented to the surgeon, on the other hand, there is most often a damaging affection which is unilateral. The surgeon considering operation must determine three things: (1) Which kidney is affected and by what variety of process? (2) how much the function of the damaged kidney is decreased, and (3) whether the function of the other kidney is sufficient to do the work of both if the damaged kidney is removed? We think that a study of the sugar in the specimens from both

kidneys aids in this work, especially when taken in conjunction with such accepted examinations as the phenolsulphonephthalein, indigo carmine, routine study and culture of the urine, together with the clinical findings.

In all, 96 pairs of specimens were examined and the results compared. It was not possible to determine accurately the condition in 24 cases, either because of insufficient data or because they are still under study. In 36 cases (38 per cent) the kidneys appeared to be normal in function, or at least as far as could be determined by usual urologic methods, there were no unilateral lesions which decreased the efficiency of either organ. (Table I.) In all of these the sugar excreted by both kidneys was singularly similar in amount. The amount of this sugar found in the urines of these supposedly normal kidneys varied from 9 mg. per 100 cc. of urine to 210 mg. per 100 cc. This sugar from pairs of kidneys did not differ more than 6 to 7 mg. in the higher figures, or 1 to 2 mg. in the lower. In those urines with the very high figures, qualitative tests done with Benedict's solution showed some reduction, and the patients were found to have an increased blood sugar. In other words, they were mild or potential diabetics. Some higher figures were also found following a meal. As has been pointed out, we know little of this substance in the blood, so that no attempt was made at this time to find out from what concentration in the blood the amounts in the urine were secreted. Of course, this may vary considerably. No special attention was paid to diet. In some cases there was a moderate difference in the amount of fluid excreted and possibly, therefore, in the concentration of the sugar. The collection time of urine from the two sides was usually equal and the amount of urine recovered was generally similar.

TABLE I.—CASES WITH BOTH KIDNEYS NORMAL AND HAVING EQUAL SUGAR

Case No.	Sugar in mg. per 100 cc.		Case No.	Sugar in mg. per 100 cc.	
	Left.	Right.		Left.	Right.
4	v. ft. tr.	v. ft. tr.	54	69	62
9	25	24	55	77	68
13	v. ft. tr.	v. ft. tr.	62	9	11
14	76	68	65	42	46
16	22	20	66	54	61
18	9	14	67	54	57
21	16	16	70	48	45
25	12	15	71	41*	56
32	36	31	73	26	30
33	17	17	80	20	17
34	141	138	82	90	100
35	86	80	83	144	148
37	210	204	84	112	120
44	26	23	86	ft. tr.	ft. tr.
45	11	9	90	ft. tr.	ft. tr.
46	33	38	93	106	112
47	17	17	99	42	44
48	17	17	100	ft. tr.	ft. tr.

* Accidentally diluted with salt solution during collection.

Usually only one examination was done on the cases with normal kidneys. One patient, however, was examined three times at intervals of about a week. Each time the sugar from both kidneys was very nearly equal, showing that the two normal organs apparently do not vary in function from time to time. The figures were for the first examination, left 17 mg. per 100 cc. urine, right 16 mg. per 100 cc. urine; second examination, left 20 mg., right 23 mg., and third examination, left 38 mg., right 37 mg.

The presence of a considerable number of B. coli in the urine without other evidence of inflammation seemed to make little or no difference in the amount of sugar excreted. These organisms were present in 6 cases when no pus or other evidences of inflammation or defective function were found. (Table II.)

TABLE II.—CASES WITH NORMAL FUNCTION AND BACILLUS COLI FOUND IN CULTURE FROM BOTH URINES.

Case No.	Sugar in mg. per 100 cc. Left.	Right.		
5	30	30		
12	14	11		
20	16	17		
40	45	46	12.30 P.M.	Apr. 1, 1929 (following lunch)
	45	45	1.00 P.M.	
	38	41	1.30 P.M.	
	17	19	2.00 P.M.	
	21	19	2.30 P.M.	
	19	17	3.00 P.M.	
	25	26	3.30 P.M.	
	24	24	4.00 P.M.	
50	49	43	May 15, 1929	
	19	18	June 11, 1929	
97	34	34		

In those patients where one kidney was apparently without function we found that the corresponding urine showed no sugar, or only a trace as compared to the urine from the normal side. Several of these kidneys were removed and found to have very little functioning tissue; they usually showed a severe hydronephrosis or infection. However, where a moderate amount of apparently functioning tissue still remained, even with lesions present, such as tuberculous abscesses, sugar from the affected side was definitely present, though much less than in urine from the normal kidney. (Table III.)

There were 4 cases in which a kidney with a decreased phenolsulphonephthalein excretion showed a definitely higher concentration of sugar than its fellow. The first time that this occurred it was thought that there had been an error in collecting the right and left specimens. In the later cases, however, the collection was made personally and with such care that no such explanation was possible. This combination accompanied, in all 4 cases, a kidney damage that was of short duration; in 3 cases a stone with temporary ureteral

obstruction and in the fourth an acute perinephric infection of about five days' standing. A possible explanation for this seems to be indicated from the work of Richards and Wearn[8,9] who found, in the frog, by quantitative examination, that chlorids and sugar were passed through the glomerular filter and reabsorbed by the tubules from the filtrate. We would suggest the possibility that the damaged renal tubules may have been unable to reabsorb all of the sugar from the filtrate, so that it was excreted in larger amount than from the good kidney.* Unfortunately, we did not do the chlorid determination on these specimens. However, in one case we estimated the urea nitrogen and found it to be, as the sugar, larger in amount from the damaged kidney. (Table IV.)

TABLE III.—CASES WITH ONE KIDNEY DAMAGED AND EXCRETING LESS SUGAR.

Case No.	Sugar in mg. per 100 cc.		Case No.	Sugar in mg. per 100 cc.	
	Damaged.	Normal.		Damaged.	Normal.
7	v. ft. tr.	15	68	22	45
8	None	12	74	25	35
11	7	25	77	30	53
19	19	51	78	ft. tr.	40
23	18	45	79	20	44
24	15	31	81	22	27
28	16	23	85	15	20
36	17	35	87	18	28
51	29	42	89	38	68
56	42	61	91	ft. tr.	100
58	8	49			

TABLE IV.—CASES IN WHICH THE DAMAGED KIDNEY EXCRETED MORE SUGAR.

Case No.	Sugar in mg. per 100 cc.		
	Damaged.	Normal.	
42	95	49	Ureteral stone with obstruction of short duration
57	56	40	Chronic pyelitis
63	63	42	Renal calculus
72	68	37	Acute renal and perinephric infection.

Mrs. E. O., following an acute attack of ureteral obstruction by calculus, excreted 34 per cent phenolsulphonephthalein on the normal side and 1.5 per cent on the damaged side. The sugar from the corresponding kidneys was 49 mg. and 95 mg. per 100 cc. of urine. It is also of interest that the urine urea nitrogen on the damaged side showed an increase over that from the normal kidney; namely, in 4 specimens 12 to 15 mg. on the normal side, 19 to 28 mg. from the damaged organ. After nine days of rest and treatment, during which a stone was passed, the two kidneys showed a normal phenolsulphonephthalein test and urine sugars equal in amount.

* Since the above was written there has appeared a paper by James A. Hawkins, Eaton M. MacKay and Donald D. Van Slyke (Glucose Excretion in Bright's Disease, J. Clin. Invest., 1929, **8**, 107) who suggest this to account for increase of urine sugar in nephritis.

It was possible to study sections from one kidney in the urine from which this condition was found.

Case Report. CASE I.—A woman, aged twenty-eight years, came to the hospital with signs of acute infection and pain in the right loin of five days' duration. Her temperature ranged from 105° to 106° F. and the white blood cell count ran about 21,000. She had had a carbuncle of the thigh several weeks previously. All other examinations were negative. A cystoscopic examination showed 1 left and 2 right ureters opening into the bladder. It was found that the left kidney excreted a urine with good phenolsulphonephthalein concentration and sugar of 37 mg. per 100 cc. urine. The right kidney, on the other hand, excreted a urine with only a trace of phenolsulphonephthalein but with a sugar content of 68 mg. per 100 cc. of urine. It seemed that this sugar might be increased in urine from an obviously damaged kidney because the affected tubules were not able to reabsorb it from the glomerular filtrate. At operation the right kidney was found to be the center of a severe inflammatory condition in which the Staphylococcus aureus was present. When the kidney was removed and the region drained the patient improved greatly. Microscopic sections of the kidney showed an inflammatory reaction at the periphery to a depth of several millimeters, and beneath that a congestion of the glomeruli with red blood cells, and marked damage to the tubules, the epithelium of which showed much necrosis.

Folin and Berglund[1] have shown that following a meal this sugar in the urine rises to an amount much above that found during the post absorptive stage. It seemed to us that a slightly damaged kidney should be able to excrete an amount of this sugar equal to the normal kidney during the post absorptive stage, but that following a meal it might not be able to take care of the increased amount normally present in the blood at this time. In order to demonstrate this it was, of course, necessary to leave the catheters in place for several hours, the cystoscope however, being removed. Several patients were examined in this way, though occasionally the presence of the catheters caused too much pain to allow of continuing the examination. The following case illustrates this point:

CASE II.—P. S., male, aged forty-two years, had a recurrent stricture of the left ureter which gave considerable pain from time to time. He returned for several dilatations. The phenolsulphonephthalein excretion was equal on both sides, and normal in amount, with no leakage into the bladder. The postabsorptive sugar amounts were: left, 20 mg., and right, 21 mg. per 100 cc. of urine. One hour after a meal, with the catheters in place, the left kidney excreted 43 mg. and the right 57 mg. per 100 cc. of urine, and one hour later the left excreted 28 mg. and the right 37 mg. per 100 cc. of urine. Apparently the defective left kidney had not a reserve function equal to the right, although it seemed able to work satisfactorily when not under a strain. The same result was found in two later examinations in this patient as well as in several other patients. (Table V.)

A case of polycystic kidneys, in which there had been some local pain, showed from the left kidney 31 mg. and from the right 23 mg. sugar per 100 cc. of urine. The diagnosis was confirmed

at operation, there being "a very large polycystic kidney on the left side and a somewhat smaller polycystic kidney on the right." The phenolsulphonephthalein examinations were normal and equal.

TABLE V.—CASE 52, SHOWING INABILITY OF DAMAGED LEFT KIDNEY TO EQUAL FUNCTION OF ITS FELLOW IN ABSORPTIVE PERIOD. FOR COMPARISON WITH THE NORMAL, SEE CASE 40, TABLE II.

Sugar.		Urea N.		
Left.	Right.	Left.	Right.	
43	57	12	18	One hour after lunch.
28	37	8	12	Two hours after lunch.
20	21	5	6	Three hours after lunch.
26	31	..	..	Four hours after lunch.

TABLE VI.—CASES IN WHICH BOTH KIDNEYS WERE DAMAGED AND PROBABLY DEFICIENT.

	Sugar in mg. per 100 cc.		
Case No.	Left.	Right.	Diagnosis.
6	52	35	Double hydronephrosis.
22	31	24	Polycystic kidneys.
26	10	11	Chronic nephritis.

Conclusions. 1. Normal urine sugars in specimens obtained by ureteral catheterization usually show approximately equal amounts of sugar from the two kidneys in the absence of any disease which damages the efficiency of either kidney.

2. Where a kidney is badly damaged the sugar is very much decreased compared with that from the normal kidney.

3. An increased sugar secretion may accompany an apparently temporary damage which is demonstrable by decreased phenolsulphonephthalein tests.

4. A slight reduction in functional efficiency may be evident only when the kidneys are forced to excrete sugar at a higher concentration, as following a meal. The damaged kidney cannot excrete urine of as high a sugar content as its fellow.

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DIABETIC KETOSIS AND FUNCTIONAL RENAL INSUFFICIENCY.

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Notwithstanding the use of insulin and the emphasis that has been placed on the diagnosis and treatment of diabetic coma, death continues to occur in patients with severe ketosis. In some instances a fatal outcome might be obviated if there existed greater knowledge of the difficulties which must be overcome to restore the patient to health. With this purpose, a study is made of the patients in diabetic ketosis admitted to the medical wards of the Presbyterian Hospital between 1916 and 1930.

This group, comprising approximately 132 instances of severe ketosis, that is, with marked symptoms and a blood CO_2-combining power of less than 25 volumes per cent, may be divided into two classes: (1) 30 patients treated before 1923 without insulin, and (2), 92 instances of ketosis treated with insulin. In the first group death was usually inevitable; there were only two recoveries from ketosis. With the therapeutic measures now commonly employed, there have been twenty-seven fatalities since 1923 in the second group. Of these, eleven seemed unavoidable; that is, 6 patients died of other diseases, including lobar pneumonia, coronary occlusion, and tuberculosis. Three other patients were admitted moribund, and 2 died suddenly from unexplained causes. Sixteen patients, while being treated with insulin, died of diabetic ketosis without complication, so far as could be determined. This investigation is made to determine the factors responsible for such fatalities.

In any such study of a considerable number of cases, the variable factors concerned are many. There were certain features of striking prognostic importance, particularly the age of the patient, the duration of ketosis before admission to the hospital, and the severity of ketosis at the time of admission. These have long been known and are apparent in most studies of diabetic ketosis. There were other signs and symptoms which were extremely variable and could not be correlated, such as adiposity, vomiting, dehydration, and starvation, and the same was true of various laboratory findings; CO_2-combining power, total base, blood and urinary acetone, blood sugar and blood fat.

There were, however, one symptom, or symptom complex, and one corresponding therapeutic procedure which in many of the more serious cases became important factors, and in some cases appar-

ently deciding factors in the ultimate outcome. This symptom complex was renal insufficiency, with particular reference to the excretion of acetone bodies; and the procedure which alleviated it was the intravenous infusions of large amounts of fluid.

The importance of the symptom complex of renal insufficiency and the effectiveness of intravenous fluids became apparent in the following way:

(*a*) In accordance with the accepted practice of the time, the group of pre-insulin ketoses were all treated by repeated intravenous infusions of large amounts of fluid containing sodium bicarbonate and sodium chlorid. This resulted in increased urinary excretion and particularly in the excretion of large amounts of acetone bodies. In the study of these cases it was noted that by this therapy the ketosis in many cases was alleviated, often for several days, and that the cases which showed greatest improvement were those in which there was the largest excretion of acetone bodies.

(*b*) On the other hand, after the advent of insulin, it became the custom to treat cases of diabetic ketosis with frequently repeated doses of insulin and glucose, together with moderate amounts of fluid by mouth or by hypodermoclysis. On analysis of this group of cases, particularly those who eventually died, it was found that there were several who on this régime failed rapidly during the first twenty-four hours after admission, with symptoms of circulatory collapse, and with the kidneys either excreting no urine at all, or else excreting urine which contained only traces of acetone bodies.

(*c*) In still another group, it was found that a rapidly failing course, such as described in (*b*) above, was often suddenly and strikingly remedied by repeated intravenous infusions, with a coincident recovery of renal efficiency and flushing out of acetone bodies in large quantities.

In this study it was seen that patients in severe diabetic ketosis might recover without insulin. On the other hand, some of those treated with insulin died of renal insufficiency. A phase of renal insufficiency that frequently puzzled was the state of ketosis without ketonuria. A factor of importance in overcoming renal insufficiency was the production of diuresis, achieved best by the use of intravenous fluids.

Relief from Ketosis Without the Use of Insulin. Previous to 1923 many patients in ketosis were temporarily relieved by infusions, only to sink deeper into coma and die of diabetes. This is demonstrated by a typical case, No. 54705.

Case No. 54705.—The patient, a housewife, aged forty-four years, had been treated for diabetes for three years. She had been drowsy for one month with some improvement from time to time. On examination she was very restless; pulse was 150, and there was acetone odor to breath. Blood sugar was 5 gm. per liter; blood CO_2-combining power was 12 volumes per cent; urine ferric chlorid test, 3+; sugar, 4+. Following intravenous

infusion of sodium bicarbonate, she became quiet and comfortable and said she felt well. Pulse dropped to 106. The improvement was only temporary and in spite of fluid forced by all routes she sank deeper into coma and died, forty-eight hours after admission. Autopsy showed nothing striking.

This illustrates what happened to a great many cases of diabetic coma before insulin, with temporary response following infusions, and subsequently steadily downhill course.

Two young diabetics demonstrated the fact that recovery from severe ketosis may take place without insulin, following a marked diuresis of acetone bodies. They are numbers 51477 and 48015.

CASE No. 51477.—The patient, a girl, aged twelve years, was admitted with a two-year history of diabetes. One year previous she had had a short period of drowsiness. The night before entering the hospital she neglected her diet and became drowsy. On admission she could be aroused, was semicomatose, hyperpneic, with strong acetone breath. Her blood CO_2-combining power was 13 volumes per cent. Urine: ferric chlorid test, 4+; glucose, 4+. During the first two days she received 40 per cent of her body weight in fluids, with large amounts of alkali and glucose, comprising three intravenous infusions in all; 3150 cc. by vein, 4550 cc. by mouth, containing 81 gm. of sodium chlorid and sodium bicarbonate. She voided 2600 cc. with 4+ ferric chlorid test. The second day she received 6000 cc. of fluid and voided 4500 cc. with 4+ ferric chlorid test. Blood CO_2-combining power rose to 24 volumes per cent and she became bright and comfortable for a week, when she again developed symptoms of ketosis while on a diet. Again, following intravenous infusions, she became comfortable. The patient left the hospital against advice three weeks after admission, improved.

CASE No. 48015.—The patient, a girl, aged nine years, had had symptoms of diabetes for only ten days. Three days previous to admission she began vomiting, became drowsy and stuporous. On examination she was found to be drowsy, but could be aroused. Breathing was deep, and acetone odor was noticed. Urinalysis: ferric chlorid test, 4+; glucose, 4+; blood sugar, 3.8 gm. per liter; blood CO_2-combining power, 10 volumes per cent; blood acetone, 1.1 gm. per liter. The patient was treated by forcing fluids and was given sodium bicarbonate and carbohydrate. She voided large amounts, containing over 20 gm. of acetone in twenty-four hours, and responded rapidly, being discharged after three weeks in the hospital, in good condition. The patient has lived a normal life for ten years, on diet and insulin, entering college, September, 1929.

Renal Insufficiency. Disturbances of kidney function have been frequently encountered in ketosis, in those treated with, as well as in those treated without insulin. Most of our patients while in ketosis showed albuminuria, cylindruria, and often an elevation of the blood urea. Many of those who recovered had been critically ill. In these instances the severe symptoms seemed associated with falling blood pressure. Oliguria and anuria often followed a paroxysm of vomiting. Two patients who demonstrated the sequence of events following a disturbance of renal function were numbers 65330 and 56481.

CASE No. 65330 (Chart I).—The patient, an American school boy, aged sixteen years, had been living on a diet and insulin for three years. Following an upper respiratory infection three days before admission, he became ill. Twenty-four hours before entering the hospital he stopped

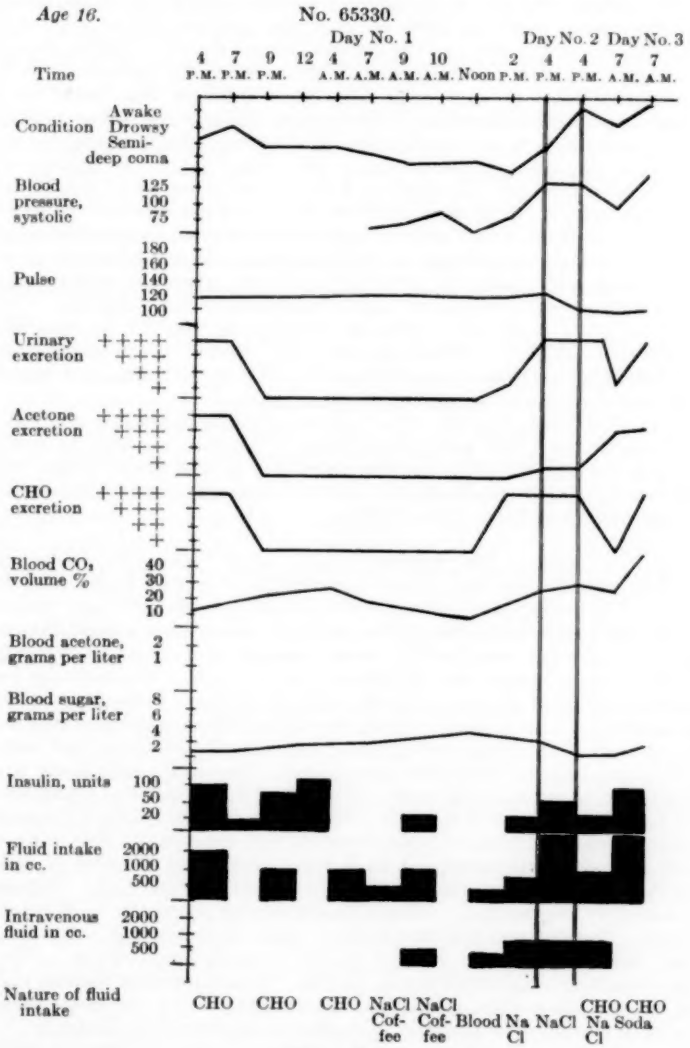

CHART I.

taking insulin, became drowsy and suffered difficulty in vision and epigastric pain. On admission, he was drowsy, pale and dehydrated, with Kussmaul breathing. Pulse rate was 120, excellent in quality. There was acetone odor and bilateral ptosis. Urine: ferric chlorid test, 4+; glucose, 4+; blood CO_2-combining power was 14 volumes per cent; blood

sugar, 3.45 gm. per liter. The patient was treated with 100 units of insulin, 2000 cc. of fluids enterally and subcutaneously, 150 gm. of carbohydrate and heat. Symptoms subsided. Three hours later, following a period of vomiting, he again became drowsy and noticed visual disturbances. Blood CO_2-combining power rose slowly to 20 volumes per cent. During the night the patient was given 200 units of insulin and 200 gm. of glucose by hypodermoclysis, receiving 2500 cc. of fluids subcutaneously. Vomiting and restlessness continued and the patient became worse. Voiding stopped in the early part of the evening, and in the morning the patient could not be aroused. Pulse became weak and blood pressure was found to be 70 systolic and 40 diastolic. Following an infusion of saline solution blood pressure rose to 84 systolic and 50 diastolic. Anuria persisted and the patient remained semicomatose. Two hours later the patient was found to be completely comatose and the radial pulse could not be felt. A half hour after a transfusion of 300 cc. the blood pressure rose to 90 systolic and 60 diastolic, and 120 cc. of urine were obtained on catheterization. An hour later the patient began to void spontaneously and became rational. Improvement was steady for twenty-four hours, when the patient again became restless, complaining of visual disturbances and vomiting. Urine was found to be sugar free, although blood sugar was 3.1 gm. per liter, later 3.4 gm. per liter. Blood pressure and blood CO_2-combining power fell. Following an intravenous infusion of 1000 cc. of saline and glucose, the patient voided and symptoms disappeared.

It was of interest that the urine following anuria contained no acetone bodies, while the blood gave a nitroprussid reaction for acetone bodies. During a period of oliguria on the third day in the hospital the blood sugar was markedly elevated and the urine gave a negative reaction to Fehling solution and Benedict solution.

CASE NO. 56481.—The patient, a girl, aged twenty-one years, was admitted, for the sixth time, in profound coma of over six hours' duration, with blood CO_2-combining power of 10 volumes per cent and blood pressure of 75 systolic and 40 diastolic. She had been drowsy for several days and omitted insulin for twenty-four hours because of nausea and vomiting. The sequence of events was as follows: 4 to 7 A.M.: No response from hypodermoclysis of glucose and 100 units of insulin. Indwelling catheter was inserted. 7 to 8 A.M.: Coma less deep following intravenous infusions of 1000 cc. of 5 per cent glucose, with insulin, 50 units, and sodium bicarbonate, 20 gm. Hypernea unchanged. Blood CO_2-combining power rose only to 14 volumes per cent. 8 A.M. to 2 P.M.: Acetone disappeared from urine at 9 A.M., and then all voiding ceased. Condition fluctuated—patient maniacal at times, deeply comatose and occasionally able to answer questions; no improvement. 2 to 4 P.M.: Following infusion of saline, moderate amount of urine was excreted, 4+; ferric chlorid test. Hypernea was definitely less marked. Blood CO_2-combining power rose to 24 volumes per cent. Patient was still very drowsy; slight improvement. 4 to 6 P.M.: Urine excretion stopped. Patient became more drowsy. 6 P.M.: Transfusion of 500 cc. of citrated blood. 7 P.M.: Blood pressure became higher than at any time since admission, urine began to be excreted, acetone present in considerable quantity, progressive improvement clinically.

It was of interest that two out of three infusions were followed by diuresis of short duration, that transfusion was followed by normal voiding, that failure to excrete acetone bodies appeared to be the harbinger of renal shutdown and that large quantities of albumin were excreted during ketosis. It was puzzling that this patient, who voided on admission and 450 cc. a few hours later, stopped excreting urine under treatment.

The first patient represented ketosis following infection with usual treatment and improvement. Circulatory renal collapse, followed by an exacerbation of symptoms, resulted in what was almost a fatal termination. Excretion of urine began, following the elevation of blood pressure after transfusion on the second day in the hospital and following an infusion on the third day in the hospital. The fall of blood pressure on each occasion came shortly after a severe period of vomiting.

The second patient demonstrated that in diabetic ketosis there may occur a disturbance of renal function, in this case characterized by a failure to excrete acetone, followed by anuria, and accompanied by falling blood pressure and aggravation of symptoms. Treatment for diabetes was of no apparent help and it was only after the elevation of blood pressure with intravenous fluids, particularly by blood transfusion, that renal function was restored and recovery took place.

Death occurred, following renal shutdown, in 16 of our patients (18 per cent) treated with insulin. These presented the appearance of circulatory renal collapse comparable to some poisonings or surgical shock, with low blood pressure and anuria. This occurred both in young and elderly patients while the underlying condition of ketosis was being attacked with carbohydrate, insulin, and fluids. The failure of the kidneys to excrete and the retention of acetone bodies formed a vicious circle resulting in death unless renal function was reëstablished, irrespective of the amount of carbohydrate burned with insulin. In those patients who were autopsied nothing abnormal was found in the kidneys. Typical examples of this downhill course were:

Case No. 66033.—The patient, a girl, aged fourteen years, had diabetes for over a year, living on a diet with insulin, 15–0–15. Four days before insulin was stopped, and thirty-six hours before she began to vomit. She had been drowsy for twenty-four hours and in coma at least sixteen hours before admission. During that period she had received 125 units of insulin without any improvement.

Examination revealed a girl in deep coma. Her blood pressure could not be read, although a slight oscillation of the mercury column appeared at 40 mm. Bladder was empty on catheterization. Blood sugar was 3.7 gm. per liter. In the hospital she was given intravenously an infusion of 1000 cc. of 10 per cent glucose and 100 cc. of 5 per cent sodium bicarbonate. Blood pressure rose to 118 systolic and 54 diastolic. She voided once—sugar, 4+; ferric chlorid test, 2+; but in spite of insulin, carbohydrates, saline, soda, stimulants and fluids by vein, she died in twelve hours, being anuric except for a short time following the infusion.

Case No. 64160.—The patient, a woman, aged thirty-six years, was known to have diabetes, but did not maintain her diet. Two days before admission she complained of drowsiness and epigastric pain. She had been in coma for twenty-four hours before admission and anuric during that period. Only 150 cc. of fluid were found in the bladder, which had collected for over twenty-four hours. In spite of intravenous glucose and saline in

large amounts she did not void. Insulin was given as well as stimulants. Blood pressure was 42 systolic. During twelve hours she received 410 units of insulin, 150 gm. of glucose, 30 gm. of sodium bicarbonate and 4500 cc. of fluid by all routes. In this period only 200 cc. of urine were obtained, which was probably a residuum in the bladder. She became steadily worse and died twelve hours after admission.

In both of these patients renal excretion was absent, and with the loss of that channel for the removal of acetone bodies, the oxidation of carbohydrate with insulin was not of apparent value.

Ketosis Without Ketonuria. Inasmuch as ketonuria is a common criterion of ketosis the absence of a ferric chlorid or nitroprussid reaction in the urine of a patient in diabetic coma, especially with a normal blood CO_2-combining power, following the administration of sodium bicarbonate, may be confusing. This condition, ketosis without ketonuria, which has been observed and reported in other clinics, occurred in 6 (16 per cent) of our patients before 1923 and in 15 (16 per cent) of those treated with insulin. All of the former died, while all of the latter presented difficult problems. Of these, 5 died without resumption of acetone excretion; 9 remained drowsy until the kidneys excreted ketones, and 1 patient with a moderate ketonemia recovered without a resumption of excretion of acetone bodies. In 3 patients with indwelling catheters, it was seen that the disappearance of acetone from the urine preceded anuria. The following patients demonstrated the sequence of events that occurred in this condition of ketosis without ketonuria.

Case No. 61852.—The patient, a colored girl, aged twelve years, had been treated at the hospital with diabetes for four years, having been in ketosis on three previous occasions. On each of these she had excreted ketones, 4+, and glucose, 4+, in her urine, and made a good recovery. She was on a diet of 130–65–140,* with insulin 25–0–15, when, following an upper respiratory infection, she became drowsy thirty-six hours before admission. On examination she was comatose; blood pressure was 120 systolic and 80 diastolic; urine showed sugar 4+ and ferric chlorid test 1+. Blood CO_2-combining power was 14 volumes per cent and blood sugar was 4 gm. per liter. During the first few hours she was treated with insulin, hypodermoclysis of saline, stomach lavage with instillation of sodium bicarbonate, urinary bladder catheterization and glucose and sodium bicarbonate by rectum. After having received insulin, 175 units; carbohydrate, 155 gm.; sodium bicarbonate, 10 gm.; fluid, 1600 cc., and sodium chlorid, 5 gm., coma became deeper. She was given an infusion of 200 cc. of 10 per cent glucose and digitalis hypodermically. Death occurred a few hours later. Necropsy showed nothing significant. The kidneys appeared normal. On the previous admissions she had excreted large amounts of acetone bodies and recovered, but in this final period of coma urine contained only slight trace of acetone, although ketosis was marked. Following the use of insulin, carbohydrate and fluid, she sank into deep coma and died within twelve hours.

* These figures here and subsequently refer to grams of carbohydrate, protein and fat respectively.

CASE No. 69774. The patient, a boy, aged seven years, known to have diabetes for three years, was admitted with a twenty-hour history of ketosis, accompanied by vomiting. He appeared hyperpneic and rather pale, yet was able to answer questions satisfactorily. Urinalysis revealed glucose 4+ and ferric chlorid test 4+. The blood sugar was 6.9 gm. per liter and the CO_2-combining power was only 12.8 volumes per cent. Eight hours later, following insulin, 70 units, glucose, 125 gm., sodium chlorid, 4.5 gm., sodium bicarbonate, 5 gm., and fluid, 2000 cc., enterally and subcutaneously, the blood sugar was 1.1 gm. per liter, and the CO_2-combining power was 40.4 volumes per cent, while the urine showed glucose 4+, ferric chlorid 1+ and nitroprussid test 2+. The patient's condition had become quite different; hyperpnea and pallor were followed by drowsiness and oliguria. Following an intravenous infusion of 700 cc. of 10 per cent glucose with 40 units of insulin, he voided large quantities (glucose, 4+; ferric chlorid test, 0). Eight hours later his blood sugar was 3.45 gm. per liter and blood CO_2-combining power was 49 volumes per cent. In spite of the rising blood CO_2-combining power, he appeared comatose, aroused occasionally only to cry. Neurologic signs, including a positive Kernig sign and stiff neck, suggested the possibility of a concomitant, central nervous system disease. Six hours later, without any treatment, he suddenly began to excrete ketones in large quantity (ferric chlorid test, 4+); simultaneously his stupor and neurologic signs disappeared.

This patient was drowsy, with an almost normal blood CO_2-combining power. Although the urine was free of acetone bodies, he was in ketosis, which did not clear up with the oxidation of carbohydrate. The excretion of acetone bodies was followed by rapid disappearance of symptoms.

CASE No. 69797.—The patient, a woman, aged twenty years, was admitted for the second time in ketosis. She was taking 65 units of insulin a day, but not adhering to a diet. Following a furuncle on her lip four days previous she began vomiting. On admission she was able to answer questions and was quite restless and dyspneic. Blood CO_2-combining power was 20 volumes per cent. Urine gave a 4+ ferric chlorid reaction and contained 5 per cent sugar. Blood pressure was 110 systolic and 60 diastolic. Following the initial infusion, the patient voided a large quantity of ketones (2.59 or 3.4 gm. per liter). During the next twelve hours, while taking 25 units of insulin each hour, adequate glucose by mouth and 1500 cc. of normal saline subcutaneously, urination ceased and her blood CO_2-combining power, which rose to 30 volumes per cent accompanied by disappearance of hyperpnea, fell to 22 volumes per cent, with the patient becoming irritable. After a second infusion the patient again voided, but only small amounts of acetone (0.096 or 0.13 gm. per liter). This specimen had a 1+ nitroprussid test and a negative ferric chlorid test. Six hours later the urine had a negative test for acetone bodies and the blood CO_2-combining power was only 22 volumes per cent. Quantitative acetone of blood done at this time showed 0.43 gm. per liter. Twelve hours later, when on a similar régime with less insulin, she voided urine with 2+ ferric chlorid and 3+ nitroprussid tests (0.6 gm. per liter). Improvement was marked and continued. Flushing the kidneys on admission removed a large quantity of ketones, and then, while under treatment, disturbances of renal function occurred. An intravenous infusion similar to the one given twelve hours before was followed by diuresis without acetone bodies. These were retained, as shown by the blood findings and the subsequent flushing of ketones.

CASE No. 64399.—The patient, a Jewish girl, aged twenty years, was admitted for the second time, having had diabetes for three years, living

on a diet of 250–80–80 with insulin. For twenty-four hours before admission she had had abdominal pain, nausea and vomiting, and became semicomatose nine hours previous to entering the hospital. On examination she was restless, uncomfortable and nauseated, with a pulse of 128 and a blood pressure of 90 systolic and 50 diastolic. Urine showed glucose 4+, but the ferric chlorid reaction was 0. Blood CO_2-combining power was 15 volumes per cent. Treatment consisted of insulin, glucose and alkalis. On admission the blood pressure was 90 systolic and 60 diastolic, the blood CO_2-combining power was 15 volumes per cent and the ferric chlorid reaction was 0. Following an infusion of 500 cc. of normal saline and glucose, with insulin, 75 units, she excreted considerable urine showing ferric chlorid reaction of 2+. Another infusion containing sodium bicarbonate was followed by similar urine excretion. The blood pressure rose, and the blood CO_2-combining power became 40 volumes per cent. The next day, while the CO_2-combining power was 65 volumes per cent, the blood pressure fell to 92 systolic and 67 diastolic. The urine gave a negative ferric chlorid reaction and the patient seemed irritable and nauseated. She was given 50 units of insulin, 1500 cc. of fluid and glucose enterally and subcutaneously. The day following she was worse. The blood CO_2-combining power fell to 25 volumes per cent. She was nauseated and vomiting. The urine still gave a negative ferric chlorid reaction. An intravenous infusion of 700 cc. of normal saline, glucose and insulin was followed by diuresis; urine giving ferric chlorid reaction of 4+. A similar infusion was followed by the excretion of 700 cc. of urine; ferric chlorid reaction, 4+. After this the pulse fell from 128 to 80 and symptoms disappeared. The patient volunteered the information that she then felt normal for the first time since admission.

This patient, while under treatment for three days, excreted acetone bodies in small amounts with a ferric chlorid reaction of 0 or 2+. She remained uncomfortable, nauseated and continued to have a low blood pressure. It was not until the third day that, following intravenous infusion, she suddenly excreted large amounts of acetone and simultaneously became symptom free.

Case No. 71851.—The patient, a boy, aged eleven years, was admitted with a three-week history suggesting diabetes. On examination he was found to be in good condition, but the blood CO_2-combining power was only 15 volumes per cent and the blood sugar was 2.5 gm. per liter. He was placed on a diet with insulin and seemed to be progressing satisfactorily, when twenty-four hours after admission he began vomiting a great deal and grew drowsy. Pulse became poor and blood pressure was found to be only 75 systolic and 50 diastolic. Although the blood CO_2-combining power had risen from 14 to 31 volumes per cent with insulin and carbohydrate, the urine, which had contained large amounts of acetone, ferric chlorid reaction 4+, acetone 9.38 gm. per liter, at this time showed ferric chlorid test 2+, acetone 2.33 gm. per liter. The blood acetone was 0.114 gm. per liter. The patient, following intravenous infusions of saline and glucose with insulin, passed large quantities of urine, but the ferric chlorid reaction became negative (acetone, 0.122 gm. per liter). For twelve hours the patient was difficult to arouse, pulse remained poor and blood pressure low. Although the urine continued to show ferric chlorid test 0, the blood-acetone content diminished from 0.114 gm. per liter to 0.052, then 0.0322 and then 0.0198, with a blood CO_2-combining power of 29 volumes per cent. Recovery was slow; the acetone bodies were cared for by the oxidation of carbohydrate with insulin.

These patients in ketosis appeared to retain acetone bodies in their tissues without excreting them in the urine. Some of them recovered promptly, following the flushing of acetone bodies. One third of these patients sank rapidly into coma, became anuric, and died. All of them presented difficult problems. There was only one recovery without a resumption of acetone excretion by the kidneys.

The Importance of Diuresis. In patients who passed but small amounts of urine, the disappearance of the symptoms of diabetic coma was usually slow. In the patients who excreted no acetone bodies, the outcome was often fatal, and in those who became anuric, death nearly always followed. In contrast to these patients, typical protocols of which have already been given, there were others who recovered satisfactorily. Among the latter the rapidity of change from coma to health appeared directly in proportion to the diuresis of acetone bodies. Characteristic cases demonstrating the effect of diuresis are:

Case No. 76234.—The patient, a school girl, aged twelve years, had been treated for diabetes for four years. For the past two years she had been on a diet of 60–60–90 with insulin, 14 units a day. She had been spilling a little sugar for a few days previous to admission. Twenty-four hours before admission she began vomiting. This continued. There was no obvious explanation for the precipitation of ketosis. On admission she was found to be extremely restless and uncomfortable. Blood sugar was 7.38 gm. per liter; CO_2-combining power was 12 volumes per cent; blood pressure was 120 systolic and 60 diastolic; urine sugar was 5 per cent and ferric chlorid reaction was 4+. She was given 20 units of insulin and an intravenous infusion of 1100 cc. of 5 per cent glucose. This was followed by small amounts of insulin and an intravenous infusion of 500 cc. containing 50 gm. of glucose, 12 gm. of sodium bicarbonate and 5 gm. of sodium chlorid. Following the first infusion, the patient voided 1100 cc. in two hours, containing acetone, 4.97 gm. In the next four hours she voided 300 cc., containing acetone, 1.1 gm. Following second infusion, she voided 200 cc. in six hours with acetone, 0.51 gm. Following two infusions, the patient practically freed herself in eight hours of ketones, voiding approximately 1600 cc., containing acetone, 6.58 gm.

This patient, having had 50 units of insulin, made a rapid response in three hours of treatment from severe ketosis to comfort, following diuresis and excretion of large amounts of acetone bodies.

Case No. 63959.—The patient, a girl, aged sixteen years, was known to have diabetes for three years and had been on a diet of 100–65–100 with insulin, 25–0–10. For twenty-four hours she had been irritable and complained of pain in the abdomen. Two hours before admission she became comatose and vomited a great deal. The cause of this break was probably an upper respiratory infection. On admission, CO_2-combining power was found to be 5 volumes per cent, blood sugar was 8.6 gm. per liter, urine ferric chlorid reaction 4+ and sugar 4+. She was treated with small doses of insulin every hour, intravenous infusions and so forth, and made an excellent response. During the first intravenous infusion, after having received 500 cc. of glucose, she came out of coma and recognized those at her bedside. At the end of the intravenous infusion (2000 cc. of 5 per cent

glucose, saline, with 20 gm. of sodium bicarbonate) she was much improved. During this period of one and a half hours she voided 1050 cc. It was thought that she came out of coma after flushing a large quantity of acetone (3.7 gm.) and then improved steadily with glucose, frequent small doses of insulin and fluid.

The Necessity of Intravenous Fluids for Diuresis. To obtain rapid diuresis the administration of insulin, carbohydrate, alkalis, fluids and stimulants was not found to be sufficient. Patients in diabetic coma or severe ketosis commonly presented a picture similar to surgical shock with a falling blood pressure and circulatory renal collapse. In these cases, fluids administered by hypodermoclysis or to the gastrointestinal tract were absorbed slowly, or not at all, and renal function ceased following a fall in blood pressure. In contrast, those measures which have proven themselves of service in overcoming surgical shock were of most help in severe ketosis. Blood transfusions proved the best agent for maintaining blood pressure; the slow intravenous infusion of large amounts of hypertonic fluids containing glucose and alkali was of great value in overcoming circulatory renal collapse and causing diuresis. The following are typical examples, demonstrating the necessity of intravenous fluids:

CASE No. 56381.—The patient, a girl, aged twelve years, was admitted for the second time with a five-year history of diabetes and increasing drowsiness of twelve hours' duration. She was on a weighed diet of 130–60–100 with 48 units of insulin before breakfast. Dietary indiscretion was probably responsible for the onset of her break. Blood sugar was 3.45 gm. per liter, CO_2-combining power was 10 volumes per cent, urine sugar was 4+, ferric chlorid reaction was 4+ and blood pressure was 50 systolic and 30 diastolic.

After receiving during the first six hours 45 units of insulin, hypodermoclysis, fluids by mouth and by rectum and sodium bicarbonate, the patient had a rise in CO_2-combining power from 10 to 26 volumes per cent and vomited, becoming more drowsy; ferric chlorid reaction, which was 4+ on admission, became 0; blood pressure fell to 50 systolic and 30 diastolic; anuria followed. At 8 A.M. she sank into coma and was then given infusion of 1000 cc. of 5 per cent glucose. Following this, the blood pressure rose; the pulse fell in a few hours from over 180 to 100; the excretion of urine began (ferric chlorid reaction, 2+) and symptoms disappeared gradually. The urine contained more and more acetone; ferric chlorid test later, 3+ and 2+.

This patient received insulin, fluids, glucose and sodium bicarbonate without any intravenous treatment. The blood pressure remained low. The patient did not excrete urine following the initial admission specimen, and sank into coma. Following an infusion of glucose, the blood pressure rose. She again voided. Ferric chlorid reaction became more strongly positive and the clinical picture became satisfactory.

CASE No. 62184 (Chart II).—The patient, a school girl, aged fifteen years, was known to have diabetes for three years. She was discharged from the hospital three years previous on a diet without insulin and later was placed on a diet of 250–75–75, with insulin 40–0–20. Seven hours

before admission she complained of abdominal pain and nausea, vomited and became drowsy. She was given 40 units of insulin. There was no definite evidence to explain the break. Examination revealed an extremely drowsy girl, difficult to arouse, with marked expiratory grunt. Blood

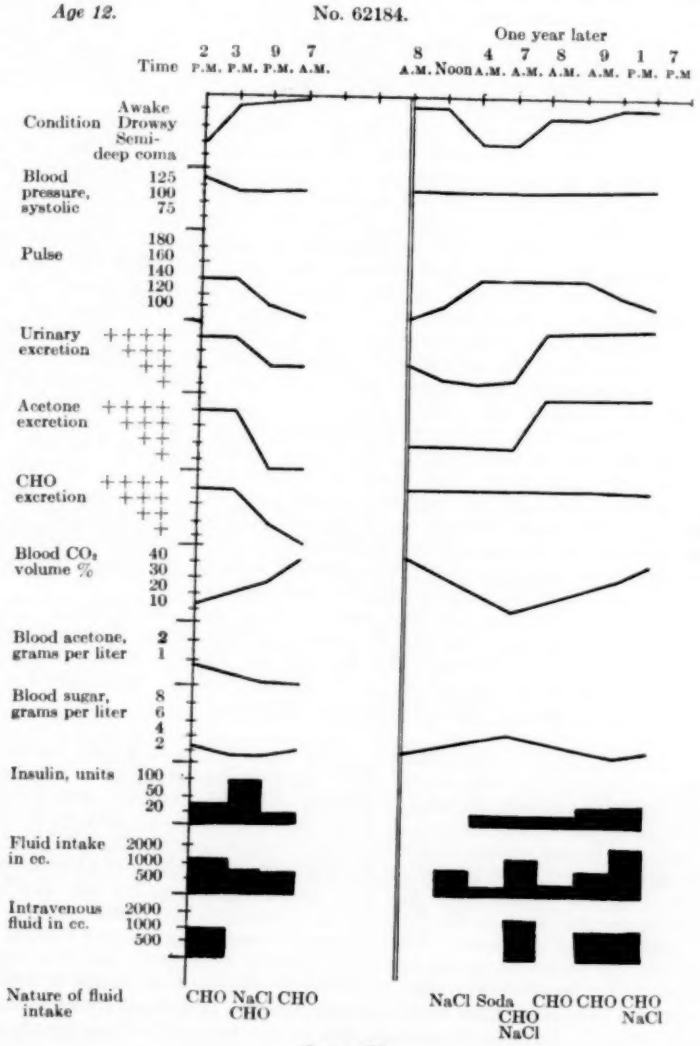

CHART II.

CO_2-combining power was 16 volumes per cent, blood sugar was 2.59 gm. per liter, urine sugar was 4+ and ferric chlorid reaction was 4+. On admission she was given glucose by intravenous infusion and saline solution by hypodermoclysis, with a moderate amount of insulin. Her blood pressure remained normal. A striking change took place immediately after the

intravenous infusion (1000 cc. of 10 per cent glucose with 50 units of insulin). She volunteered the information that the pain had gone and recognized those at the bedside; skin became warm and cyanosis disappeared. Within an hour she voided 550 cc. Hyperpnea persisted for three hours. When infusion was given on admission blood acetone was 0.75 gm. per liter. About one hour after infusion patient voided 550 cc.; ferric chlorid reaction, 4+. Four hours later blood acetone was 0.25 gm. per liter and blood CO_2-combining power was 28.4 volumes per cent. Urine ferric chlorid reaction was negative after the first diuresis. Twelve hours later blood acetone was almost absent.

Clinically it seemed that rapid changes followed the diuresis of ketones.

The same patient was readmitted the next year. On a similar diet she now required 50 units of insulin, when previously she had taken 110. There was a spilling of a small amount of sugar. Two days before she became nauseated and vomited. There was no evidence that explained precipitation of ketosis. She was admitted in fairly good condition to have her diet regulated. Her blood pressure was 120 systolic and 100 diastolic, blood sugar was 1.02 gm. per liter, blood CO_2-combining power was 40 volumes per cent, urine sugar was 4+ and ferric chlorid reaction was 2+. She was given a hypodermoclysis of saline solution and water by mouth. Twelve hours later the patient was markedly restless and hyperpneic, with Kussmaul breathing and severe abdominal pain. Blood CO_2-combining power had dropped from 40 to 12 volumes per cent. Condition became serious. Thus, after having a hypodermoclysis of 1000 cc. of saline and having had sodium bicarbonate, 10 gm., by mouth, with no vomiting, she slipped into semicoma. Following an intravenous infusion of 1500 cc. (saline and 5 per cent glucose) she voided 1050 cc., containing 4.5 gm. of acetone. Two more intravenous infusions and moderate doses of insulin were followed by the excretion of 0.76 and 0.36 gm. of acetone. After each diuresis the symptoms rapidly disappeared, that is, Kussmaul breathing, drowsiness, headache, pain in stomach and nausea.

This patient on two occasions responded clinically to diuresis. Fluids given by other route in the second instance were followed by development of ketosis. On the first admission she did well after an infusion. On the second admission she did poorly after hypodermoclysis, went into a coma and recovered quickly after intravenous infusion.

Case No. 59106.—The patient, a girl, aged four and a half years, had been admitted one year before with diabetes had weathered a series of infections (diphtheria, measles, tonsillitis, Vincent's angina) and lived on a diet of 40–60–90 and insulin, 15–0–5. She contracted a cold a week before admission, began spilling sugar and was brought into the hospital to have her diet arranged. On admission she was quite well. Blood CO_2-combining power was 30 volumes per cent and blood sugar was 3.7 gm. per liter. During her ten days in the hospital she continued to excrete acetone and glucose in large amounts. When diet was being changed and insulin was omitted for twelve hours she became markedly hyperpneic and was treated at once for impending coma, receiving in twenty-four hours a total of 220 units of insulin, 1200 cc. containing 120 gm. of glucose by hypodermoclysis, 300 cc. of glucose by rectum, 400 cc. of 5 per cent sodium bicarbonate by rectum and orange juice and sodium bicarbonate by mouth. She did not receive any fluid intravenously and vomited almost every hour, over fifteen times altogether. No urine was obtained with indwelling catheter. Anuria existed for twelve hours; pulse rose from 100 to 180. The blood CO_2-combining power was 80 and 50 volumes percent, yet she died after one day of ketosis.

In this patient with a normal blood CO_2-combining power, receiving

insulin, carbohydrates and fluid in large amounts, but none intravenously, the kidneys shut down and the patient died in ketosis.

CASE NO. 224211.—The patient, a maid, aged nineteen years, was sent to the hospital as a case of poisoning, having been in deep coma for eight hours. She was not known to have diabetes mellitus; however, on catheterization her urine was found to contain glucose, 4+, and gave a ferric chlorid reaction of 1+. Examination revealed a pale girl in deep coma with extreme hyperpnea, tachycardia and marked odor of acetone to the breath. There was a cutaneous infection about the vagina. The blood pressure was systolic 138 and diastolic 90, the blood sugar was 5.16 gm. per liter, the blood CO_2-combining power was 13 volumes per cent and blood acetone was 1.21 gm. per liter.

The patient was given 40 units of insulin and 1000 cc. of 10 per cent glucose intravenously, followed by 1000 cc. of normal salt solution containing 20 gm. of soda. An indwelling catheter was inserted. During the infusion she excreted 1300 cc. of urine containing 5.56 gm. of acetone. Simultaneously she began to arouse. The blood acetone rose to 1.34 gm. per liter. Ten units of insulin were given every half hour and more intravenous fluids, consisting of 1000 cc. of 10 per cent glucose and 1000 cc. of saline. Following this infusion, she excreted 1900 cc. of urine, containing 10.37 gm. of acetone. During seven hours she changed from almost a moribund condition to a mental state which was nearly clear. During that time she voided 3200 cc., containing 15.93 gm. of acetone, although on admission her urine was nearly free of ketones. The blood acetone fell to 0.62 gm. per liter and the blood CO_2-combining power rose to 27 volumes per cent.

For twelve hours the patient was treated with glucose and orange juice by mouth, receiving 2660 cc., containing 80 gm. of glucose, and was given 10 units of insulin every hour. Although her blood pressure remained elevated and the blood CO_2-combining power had risen to 37 volumes per cent, the urine flow became scanty. It contained glucose, 4+ and gave only a 1+ ferric chlorid reaction. Vomiting began and the patient sank back into a semicomatose state. During intravenous infusions, consisting of 3000 cc. of saline and glucose, she excreted a large quantity of urine giving a 4+ ferric chlorid reaction. Simultaneously with her diuresis, she became mentally clear and subsequently made an uneventful recovery.

This patient made a prompt recovery from deep coma following infusions. The urine, which showed only a slight ferric chlorid reaction before the injection of fluids intravenously, contained large quantities of acetone during the diuresis. Subsequently, while taking adequate amounts of fluid and carbohydrate by mouth, with the necessary insulin, kidney excretion diminished, the urine showed again only a faintly positive ferric chlorid reaction, and the patient sank back into coma. Once more, following infusions, large quantities of acetone bodies were excreted and recovery was prompt.

These patients were examples that demonstrated the importance of administering fluids intravenously rather than by other routes.

Conclusion. 1. In the alleviation of acute ketosis urinary excretion of acetone bodies is of perhaps greater importance than their oxidation.

2. It has been repeatedly demonstrated in the group of patients presented that ketonemia may exist in absence of ketonuria. This condition appears at times to precede anuria and should be regarded as a warning to the physician.

3. The development of anuria greatly jeopardizes the recovery of a patient with severe ketosis.

4. Intravenous fluid has been of far greater value in causing excretion of ketone bodies and in correcting anuria than fluid administered by other routes.

5. Recovery from severe ketosis may depend largely upon the rapidity with which acetone bodies are excreted by the kidney, and may be prevented by the development of functional renal insufficiency.

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THE PROBLEM OF PULMONARY TUBERCULOSIS IN PATIENTS WITH DIABETES.

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For many years it has been generally known that coma, vascular disease, including gangrene, and infections, including tuberculosis, have been the chief causes of death among patients with diabetes. Insulin has done much to do away with the dangers of coma. Almost every doctor at all interested in following up his diabetic cases has

several on record of recovered coma and it is not uncommon to meet individual diabetics who have been in deep coma on three or four occasions.

Gangrene, also, has been attacked with almost as striking results. While diabetic gangrene still causes many deaths, its immediate mortality is much less than in the pre-insulin days. Sensible preventive measures have been devised; patients are routinely taught, for example, to take the most punctilious care of even the slightest abrasion occurring on the hand or foot, and almost all have been warned that the loss of an arm or leg may be the penalty for needless glycosuria and a neglected scratch. Insulin certainly has done much to allow older diabetics to keep well and comfortable.

Infections are still dangerous. Of these, the acute self-limited infections like pneumonia or typhoid fever are far less of a menace to the diabetic on the whole than is such a chronic, insidious infection as tuberculosis. It is my purpose in this paper to review the clinical experience of the Medical Clinic of the Peter Bent Brigham Hospital, with pulmonary tuberculosis in diabetes, so as to awaken interest in behalf of the tuberculous diabetic, and to demonstrate that in diabetes, pulmonary tuberculosis is not a particularly rare complication and is often one of uttermost severity.

The Medical History of Tuberculosis in Diabetic Patients. Pulmonary tuberculosis has been recognized as a significant complication of diabetes for a long time. Probably Richard Morton[1] deserves credit for drawing attention to the importance of the subject by making the first case report in 1694. The matter has been discussed subsequently in a variety of ways. For instance, early in the nineteenth century the French investigators Nicolas and Gueudeville[2] were so impressed with the incidence of tuberculosis and diabetes as to write a monograph on "la Phtisurie Sucrée," while a few years later in England, Copland and Bardsley[3] stated that tuberculosis occurred so frequently in diabetes as to be a sign of this disease.

There have been published four theses from the University of Paris on the general subject of diabetes and tuberculosis. The first was in 1873 by Bertail,[4] the second in 1888, by Bagou,[5] the third in 1895, by Sauvage[6] and the fourth in 1926, by Péronne.[7] The time interval elapsing between these various publications is of interest, mirroring very fairly the changing fashions by which the various problems of diabetes have been approached. It was from 1870 to 1900 that the clinical aspects of diabetes appeared of greatest importance to the researcher. The method of clinical and pathologic correlation was generally employed and investigators were endeavoring to discover a definite pathology which might explain the complex clinical findings of diabetes.

From 1900 to the discovery of insulin there followed a period in which new laboratory methods were developed with great rapidity.

These were applied to the study of diabetes and resulted in explaining many of the chemical and physiologic reactions of this disorder. During these years, the strictly clinical aspects of diabetes appeared of relatively little interest, and clinical-pathologic studies on diabetes appeared less often.

The introduction of insulin in 1922, has reawakened, apparently, a new interest in the clinical phenomena of diabetes. Perhaps this depends on the fact that our diabetic patients are now living longer than they were and thus have greater opportunity to develop unusual complications, or perhaps Banting's discovery, emanating from a clinician, has stimulated other clinicians to investigate their cases more thoroughly. In any event, interesting and carefully written papers on various clinical or pathologic phases of diabetes are again appearing and are being published more frequently than they were a few years ago.

Recent literature on the subject of diabetes and tuberculosis is voluminous and very bewildering, especially in relation to the manner in which the tuberculous diabetic is affected by insulin. One can obtain all sorts of conflicting opinions. LeNoir and Scherrer[8] have been able to divide roughly the recently published literature into three groups: there are authors who claim that even small doses of insulin may activate an inactive tuberculosis in a diabetic patient or may exaggerate the fever of a tuberculous diabetic and thus be injudicious to use; there are authors who believe that insulin has no particular effect on the course of tuberculosis in diabetes; and, finally, there are authors who believe that insulin can be definitely helpful in treating this particular combination of diseases.

If one were to make any general criticism of the already assembled literature, it would be that recent writers on diabetes and tuberculosis have tended to report but small groups of cases, followed for but short periods of time by any given method of treatment, and have failed to assemble any relatively large group of such cases carefully followed for a sufficiently long time to properly emphasize the life history of this combination of diseases.

The Seriousness of Diabetes and Tuberculosis. Wilder and Adams[9] have been kind enough to send me the following statistical data from Rochester: Among the first thousand cases of diabetes studied at the Mayo Clinic after 1922, when insulin became available for general clinical use, there were 25 entering with gangrene, 29 entering with sufficient acidosis to produce a blood bicarbonate concentration of less than 25 volumes per cent and 10 entering with signs of active pulmonary tuberculosis. At the date of their letter, a little more than four years after the thousandth case was seen, and a little more than seven years after the first case was studied, 10 of the group with acidosis (34 per cent) are dead, 16 of the group with gangrene (64 per cent) and 7 (70 per cent) of the group with pulmonary tuberculosis. In other words, these figures suggest that in

any large group of diabetics, there will inevitably appear a certain number complicated by acidosis, gangrene and pulmonary tuberculosis. If the cases are followed for a sufficiently long period of time after they are first observed, it will become evident that an attack of diabetic acidosis has no profound effect on a patient's life expectancy. A patient who has gangrene may escape death during the immediate attack but is unlikely to live for many years thereafter. A patient who is unfortunate enough to contract pulmonary tuberculosis will probably succumb to his combination of diseases with disheartening rapidity. Of these three major complications of diabetes, infection in the form of pulmonary tuberculosis is, at present, by all odds the most serious.

The Incidence of Pulmonary Tuberculosis in Diabetes. In the Peter Bent Brigham Hospital and its Outdoor Department from October 1, 1922, to January 1, 1929, there appeared 1529 patients with diabetes, and of these 35 had or developed subsequently active pulmonary tuberculosis. Joslin[10] reports 43 cases among his last published 3000 cases. Combining the figures of Wilder and Adams with these, it appears that in a group of more than 5500 diabetics the incidence of pulmonary tuberculosis was approximately 1.6 per cent. Admitting that there are upward of a million diabetics in the country alive today, there must be approximately 16,000 with tuberculosis to be taken care of, a sufficiently impressive number to demand serious consideration.

It has been suggested that all patients with diabetes are particularly prone to develop pulmonary tuberculosis, and this may be true. Joslin has reported the age incidence at time of onset of 2611 cases of diabetes observed in his clinic, and Adams,[11] similar data from 1000 cases in the Mayo Clinic. Diabetes develops in people of all ages from infancy onward, but is found most frequently in adults at about the age of fifty years. Tuberculosis, too, develops in people of all ages. The age incidence of active tuberculosis in the Peter Bent Brigham Hospital group of diabetic patients is not unlike the age incidence of diabetes in the combined series of Joslin and Adams. Tuberculosis, fortunately, is not often encountered in young diabetics and tends to be seen more often in the elderly ones. On the whole, however, one gets the impression that tuberculosis develops most easily where it has the best opportunity; it is relatively uncommon in young diabetics because diabetes is a relatively rare disease in youth and more common among older diabetics because there are so many more of them in existence to have a chance to become infected.

The Cause of Tuberculosis in Diabetes. There are perhaps many reasons why a person afflicted with a wasting disease like diabetes might acquire tuberculosis. The records of the Brigham Hospital cases have been analyzed in an attempt to discover some specific reasons why our particular cases should have picked up the com-

plicating infection. No definite conclusions can be drawn but one gathers some interesting impressions.

In the 3000 cases reported by Joslin there were 43 cases of tuberculosis or about 14 in each thousand. Wilder and Adams saw 10 cases of tuberculosis in 1000 cases. In our series of 1529 diabetics were 35 cases of tuberculosis or about 23 per thousand. Evidently we have met with a higher proportion of tuberculous cases than have Joslin or the Mayo Clinic. In all probability this discrepancy depends on differences in social conditions of the various groups of cases. The Peter Bent Brigham Hospital cares largely for the poor of Suffolk County in Massachusetts, while Joslin and the Mayo Clinic draw patients from all over the world and do not deal so exclusively with people of straitened means. It appears that the needy diabetic is the most liable to develop tuberculosis and on this account requires especial assistance.

In most of our cases the diabetes was known to exist for some time previous to the development of the pulmonary tuberculosis, although in several, both diseases were first recognized at the same time. In a few cases, as judged by Roentgen ray, there was an old tuberculosis which flared up as a late complication of diabetes. In general, therefore, the tuberculosis of diabetics is an acute fresh process and but seldom is grafted on an old quiescent infection.

The occupations of our group varied very widely but one striking fact is that 74 per cent were employed in some form of indoor sedentary work. Properly supervised exercise is now recognized as an important adjunct to good diabetic therapy, and perhaps may even help to serve as one of the means of preventing the development of tuberculosis in diabetes.

The family histories of our cases are of some interest. Eleven of the group (31 per cent) had tuberculosis in their families and 5 (14 per cent) diabetes. Two cases (6 per cent) had a family history of both diabetes and tuberculosis. In 17 cases (49 per cent), however, there was no known history of either diabetes or tuberculosis. Thus direct contact or a familial tendency to either diabetes or tuberculosis did not appear of striking importance.

Most of our patients at one time were obese, and rapid loss of weight appeared to be the most constant single factor through which both diseases became recognized. On the whole, a stout rather elderly person, in poor circumstances, possibly with a family history of either diabetes or tuberculosis, leading a sedentary indoor life without exercise and developing diabetes which was untreated and accompanied by a rapid loss of weight, appeared to be the most likely candidate to succumb to a complicating tuberculosis.

The Importance of Adequate Treatment in Diabetes. Our cases fall into two distinct groups: there were 11 cases (30 per cent) which developed tuberculosis while under treatment for diabetes and 24 (70 per cent) which were discovered to have active tuberculosis at

the time they were first seen in the Brigham Hospital Clinic. The fact that so large a proportion of the cases developed tuberculosis while under observation is of course very striking and deserves special comment.

Carelessness in treatment plays havoc with a diabetic. Most of our cases which developed tuberculosis while under observation did so through lack of properly supervised treatment. It is difficult to formulate any definite description of an ideal treatment for diabetes and even more difficult to carry out anything approaching an ideal treatment in outpatient work. It is apparent, however, that any doctor or clinic undertaking to care for diabetic patients must employ some system of follow-up work by which the patients are examined systematically at frequent intervals and are kept track of for long periods of time. The case which does not improve must be suspected of having tuberculosis. Every diabetic patient owes himself repeated examinations each year as well as routine blood-sugar determinations and urinalyses.

The Diagnosis of Pulmonary Tuberculosis in Diabetes. It was formerly my impression that pulmonary tuberculosis may be difficult to recognize in diabetic patients. Yet a careful review of the records of the Peter Bent Brigham Hospital cases does not bear out this impression. For several years we have had Roentgen ray films made of the chests of almost every diabetic patient that came to the hospital. In 1927, Sosman and Steidl[12] reviewed the radiologic findings of 17 of our cases and found that hilum infiltration was evident in every instance. In the early stages, on this account, tuberculosis may be difficult to recognize clinically.

If one goes over our clinical records from the viewpoint of physical signs, however, it appears that regardless of how the process began, most of the cases developed in a short time the common physical signs of pulmonary tuberculosis with dullness at either or both apices, with râles and with positive sputum—provided the sputum was examined with sufficient care. It is fair to say, therefore, that if looked for in the diabetic, tuberculosis can be easily recognized in most instances. No doubt it is useful and important to have Roentgen ray films of a diabetic's chest, but because of the Roentgen ray, careful physical examination is by no means an obsolete diagnostic method.

The Prognosis of Tuberculosis and Diabetes. The ultimate prognosis of diabetes and tuberculosis, as judged by our experience, as well as by that of others, is not good. Of our 35 cases recognized from October, 1922, to January, 1929, 30 (86 per cent) are now dead. This figure in itself demonstrates how ominous is this particular combination of diseases, for nowadays patients with uncomplicated diabetes are expected to live as long as anyone else. When the tuberculosis is discovered, its subsequent course is often rapid and progressive in spite of all effort. According to our experience,

the usual duration of a diabetic patient's life after an active pulmonary tuberculosis is once discovered is illustrated in the following table:

TABLE I.—THE DURATION OF LIFE IN DIABETES AFTER TUBERCULOSIS IS RECOGNIZED.

(30 FATAL CASES.)

One year or less	19 cases (63 per cent)
More than one year and less than three years	7 cases (23 per cent)
More than three years	4 cases (13 per cent)

Certain cases get well but they must be rare. We have seen but one with this good fortune. A man, aged fifty-two years, came to the Outdoor Department in October, 1927, weighing 160 pounds and with diabetic symptoms of about a year's duration. A Roentgen ray of the chest revealed no abnormality.

He was advised to eat a diet which did not keep him sugar free but which resulted in making him lose 20 pounds in weight during the following three months. During this interval he developed cough, chest signs, positive sputum and a lesion at the right apex. As measured by Roentgen ray the process extended as low as the level of the fourth rib.

When the tuberculosis was recognized the man was treated in a less haphazard fashion. He was put in bed at absolute rest for a period of six weeks, and was then advised to resume his activities very conservatively. He was given a liberal diet and enough insulin to prevent glycosuria. Now, more than two years later, he has no signs of tuberculosis. Physical and radiologic examinations are negative and the diabetes is controlled.

Our cases bring up another practical point in prognosis. Of the four patients which have lived the longest after active tuberculosis was discovered, three gave evidence, by their histories or radiologic examinations, of having an obsolete pulmonary lesion which had become reactivated. Sosman and Steidl have commented on the dangers of the acute type of tuberculosis which they observed so frequently. This appears to have the worst prognosis. Perhaps an old focus of tuberculosis in a diabetic may protect that patient later from so virulent an infection as may develop in those diabetics unfortunate enough to acquire tuberculosis. The finding of old lesions by Roentgen ray in a diabetic's chest, therefore, is a good sign rather than a bad one, and even though the lesion becomes active, the prognosis is not as bad as in those cases with an entirely fresh process.

The Treatment of Diabetes and Pulmonary Tuberculosis. There is little to be said about the treatment of diabetes and tuberculosis. The patients certainly require the best of diabetic care, an adequate diet, and sufficient insulin to keep the urine sugar-free. They also require the best of care for tuberculosis with rest and fresh air for a

long period of time. Pneumothorax in one of our cases was not helpful.

Most of our patients were sent to one of the sanitaria after a period of observation in the Peter Bent Brigham Hospital. Follow-up notes by the various doctors who cared for them in various ways later, are all of much the same tenor. In spite of any therapy the tuberculosis advanced and the patients died. I can discover no reason for thinking that insulin was in any way harmful as a therapeutic agent to any case, nor that the tolerance of any increased during the course of the tuberculosis in such a remarkable fashion as to suggest the formation of parainsulin according to the idea of Lundberg.[13]

Summary and Conclusion. On the whole, the complication of pulmonary tuberculosis is indeed a serious one for the patient with diabetes. At the present time there are probably in the neighborhood of sixteen thousand diabetics in this country afflicted with active pulmonary tuberculosis and of these more than half are likely to die within the first twelve months after the correct diagnosis is established.

Pulmonary tuberculosis is particularly prone to develop in the elderly diabetic, of poor circumstances, leading a sedentary life, who has been at one time obese and through inadequate treatment for diabetes has lost weight rapidly. The tuberculosis may begin deep in the hilum region of the lung and at first may cause no signs or symptoms. Before long, however, the tuberculous diabetic will develop the usual signs of pulmonary tuberculosis with positive sputum. The pulmonary lesion in its beginning may be unrecognizable except by the Roentgen ray, but later can be detected easily by ordinary physical diagnosis.

Tuberculosis may develop in a diabetic patient while the patient is under treatment. It is very important for any doctor or clinic treating diabetic patients to remember this and to be on the lookout for a developing pulmonary tuberculosis. A patient under treatment for diabetes who does not hold his weight or who does not appear to be getting along satisfactorily should be suspected of having tuberculosis. All diabetic patients should be watched carefully and should have repeated physical examinations from time to time in order to forestall future complications.

The treatment of pulmonary tuberculosis according to the experience of the Peter Bent Brigham Hospital cases is unsatisfactory. At best, it is time consuming and expensive, for it requires unlimited rest, fresh air, and, in addition, adequate diabetic treatment for a long period of time. There may be apparent temporary improvement under any appropriate therapy but the final prognosis is poor. Our cases which lived the longest were those which had a quiescent pulmonary process antedating the diabetes. Later this became active, but was more amenable to treatment than the fresh type of

tuberculosis developing as a late complication of diabetes in an unresistant individual.

In future it may be possible to establish preventive measures against the occurrence of tuberculosis in diabetic patients. The first step in such a campaign, however, is to admit that at the present time tuberculosis is not infrequently encountered in diabetic patients, that it is often overlooked and treated improperly, and that it is an extremely grave complication. Cases must be recognized earlier than they are recognized at present, they must receive more serious consideration than they receive at present by doctors in the country at large, and once recognized, they must be given immediately all the benefits of the constantly improving methods of treatment which are being developed in the independent fields of the two diseases.

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SOME OBSERVATIONS ON MITRAL STENOSIS AND MEASUREMENTS OF NORMALS AMONG CHINESE.

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During the last few years several Chinese patients with questionable signs of mitral stenosis were seen in this hospital. Neither roentgenogram nor electrocardiogram permitted any more definite

interpretations than the other physical findings,[23] nor did the subsequent course of the cases which could be followed add any information. But it became obvious that any attempt to draw a line between normal and pathologic findings should be preceded by a survey of the available material on both sides of the border. This survey comprised:

1. Study of the records of hospital patients with mitral stenosis, especially with regard to possible etiologic factors and prominent clinical features.

2. Mensuration and the taking of roentgenograms and electrocardiograms of normal young Chinese adults.

Mitral stenosis is often overlooked, especially in the early stage. The well-known diagnostic difficulties are best illustrated by Cabot's[2] statement, which is in keeping with observations of other authors; namely, that less than half of the autopsied mitral stenosis cases obtained from all services of the Massachusetts General Hospital were properly diagnosed during life.

Enlargement of the heart in a young adult implies, even in the absence of auscultatory findings, the possibility of mitral disease. To be of greatest benefit the diagnosis should be established before cardiac enlargement indicates serious, and usually, irreparable damage.

Besides the early mitral lesion of rheumatic origin there are two rarer conditions recorded in literature in which the heart, as a rule, is found to be normal or small in size, at least before complications arise, namely, Durozier's disease and spasmodic mitral stenosis. Durozier's disease, also called pure or congenital mitral stenosis,[1, 31] gives the anatomic picture of a sclerosis of the mitral valve, often involving the pulmonary artery as well. The patients, mostly women, usually show signs of general underdevelopment. Pulmonary manifestations, especially hemorrhages, are very prominent in the clinical picture. In some of the patients tuberculosis or congenital syphilis have been encountered, but the etiologic importance of these chronic infections has not been proved.

Under the name functional or spasmodic mitral stenosis, Bard and others[1, 21, 27, 31] have described cases in which palpatory and auscultatory signs of mitral stenosis are present only in a slight degree and not permanent. The patients often show signs of endocrine disturbances. The interpretation of the physical findings naturally remains somewhat hypothetical.

Differential diagnosis is of importance because the rheumatic lesion with its tendency to recrudescence will require a management different from that of Durozier's disease, which usually represents a stationary valvular defect; and the—hypothetical—functional mitral stenosis will require only such advice as may influence any underlying general condition.

Survey of Hospital Records. Among 24,000 patients admitted to this hospital during seven and one-half years, 95 men and 62 women were found to have mitral stenosis, as a single or combined valvular lesion. Meleney and Kellers[18] call it the most common heart lesion in North China, and Dieuaide[8] comments upon its surprising frequency. Meleney and Kellers in 1924 have reviewed the histories of 35 Chinese patients with mitral stenosis and have commented on the low incidence of typical rheumatic fever, and from subsequent observations on a larger scale in this hospital the impression is gained that severe involvement of the joints so familiar to American and British writers is very rarely seen among Chinese afflicted with rheumatic fever.

In the present survey, which includes Meleney and Keller's cases, no attempt was made to discriminate between a history of swollen joints and pains in the extremities marked enough to implant itself in the patient's memory. So-called growing pains and fleeting transient joint affections are even more characteristic of rheumatic fever than marked arthritic manifestations.

Duckworth's[18] rheumatic antecedents, namely, rheumatic fever, arthritis and chorea, were recorded in the past history of this series in about the same percentage (46 per cent) as stated by Meleney and Kellers. This conforms with the figures reported from Romberg's[24] and Plesch's[22] 1500 cardiac cases in Munich and Berlin respectively, but contrasts with Cabot's observation of 78 per cent rheumatic arthritis and 6 per cent chorea, that is, 84 per cent, or with Duckworth's 70 per cent rheumatic antecedents.

Naturally anamnestic data are an even more precarious basis for differentiation between the various forms of acute joint affections than actual clinical observation would be ———— a source of error common to all statistics mentioned above.

A frequent manifestation of mitral stenosis found in this series was hemoptysis. About 40 per cent of the patients stated that they had either frank spitting of blood or only blood-streaked sputum. Chien[3] commented upon similar observations among Chinese from Changsha. Cabot found in almost half of his autopsies evidence of pulmonary infarction, although his clinical material showed a much lower incidence of hemoptysis.

In our series of cases careful and usually long observation ruled out any important pulmonary tuberculous lesion. Only 17 out of 162 cases showed shadows in the roentgenogram suggestive of hilum or minimal tuberculosis. Only 9 of these 17 had had hemoptysis. If we further compare this incidence of a little over 10 per cent with the incidence of 17 per cent as found in routine roentgenograms of 350 doctors, students and nurses examined in this hospital during the last eight years, it does not seem probable that the hemoptysis in our cases was, as a rule, due to pulmonary tuberculosis.

The incidence of syphilis among these patients—the diagnosis

based on a positive Wassermann reaction—of 14.2 per cent was not higher than found in previous surveys among medical patients and healthy employees.

As Meleney and Kellers have stated in their survey the cases of the present series are as a whole to be classified as rheumatic heart disease.

In three instances history and physical findings resembled those described by Durozier, but verification by autopsy was not available. In the 16 autopsies of this series obtained so far in this hospital, distribution and gross appearance of the valvular lesion did not differ essentially from the picture of rheumatic heart disease. Aschoff bodies were recorded in 4 of the 16 cases of long-standing.*

Table I.—Hospital Records.	Males.	Females.
Rheumatic fever or joint pains or chorea	28	15
Hemoptysis	21	14
Positive Wassermann reaction	6	2
Rheumatic antecedents and hemoptysis	13	7
Rheumatic antecedents and positive Wassermann	1	2
Hemoptysis and positive Wassermann	4	1
Rheumatic antecedents, hemoptysis and positive Wassermann	4	2
Negative history	18	19
Wassermann not done	4	7
Total	95	62

Males.	Per cent.
Rheumatic antecedents in 46 cases	48.6
Hemoptysis in 42 cases	44.2
Positive Wassermann reaction in 15 out of 91 cases	16.5

Females.	Per cent.
Rheumatic antecedents in 26 cases	42.0
Hemoptysis in 24 cases	38.7
Positive Wassermann reaction in 7 out of 55 cases	12.7

Mensuration of Normal Chinese. During the last twenty-five years an increasing number of observers has emphasized the coincidence of certain types of cardiac measurements and electrocardiograms with certain constitutional features. From the various methods of mensuration Martinet's[16] morphologic index (M.I.) was chosen as a simple and sufficiently accurate expression of the individual habitus or build.

$$\text{Martinet calls M.I.} \quad \frac{\text{height}}{\text{biaxillary diameter.}}$$

The biaxillary diameter is measured by a ruler to which branches are attached at right angles. These are held by the subject in both axillæ with the arms hanging down while in expiration. The ratio given by Martinet is:

(*a*) Below 5.5 for the brevilinear (stocky) type.
(*b*) 5.5 to 6 for the mediolinear (average) type.
(*c*) Above 6 for the longilinear (slim) type.

* An object of further study.

In the present series the biaxillary diameter was determined in a way somewhat different from that introduced by Martinet. Calipers were used and the transverse diameter determined in the intermediate respiratory phase. It was taken at the level of the fourth sternocostal junction in accordance with the agreement for international measurements (Duckworth)[9]. Our index figures would therefore be expected to be at a slightly lower level than if measured by Martinet's original method. In our use the term morphologic index should therefore be understood with this modification in mind.

One hundred and fifty apparently healthy young Chinese adults, 105 men and 45 women, were selected for these examinations from our students, nurses and doctors. Their birthplaces comprised nearly all of the provinces of China, a few were born on the Pacific islands or on the American continent. Their ages varied between nineteen and thirty-four. None of them had been under observation for less than one year, the majority for several, up to eight years. Among them only one brevilinear and 12 mediolinear subjects were found. The rest of the 137 longilinear indices were evenly distributed between the sexes in the proportion of their numbers at the various levels. (See Charts II and III.)

Roentgenograms of Normal Chinese. Roentgenologic examination consisted of the three usual methods: (1) fluoroscopic examination; (2) stereoscopic chest films at 5 feet distance and (3) a teleoroentgenogram of the heart at 2 meter distance, exposure one-tenth second with the subject facing the film and breathing quietly. Orthodiagrams were not available.

The composite heart size was found to be slightly smaller—less than 3 sq.cm. per person—than the average size computed for Americans from height, weight and age.[11, 12] In these statistics it was found that the subjects were divided with respect to the foreign standard of heart size as shown below.

		Relation to American standard.		
No.	Sex.	Above.	Normal.	Below.
105	Males	28	12	65
45	Females	13	4	28

Fourteen men and twelve women showed a marked dextroposition of the heart with 40 per cent or more of the horizontal diameter being found to the right of the midline.

Vertical position or cor pendulum, of varying degrees, was pronounced in about one-third of the cases. It was attempted to express the degree of "verticality" by the size of an angle V between the midline and a line drawn from the cardiac apex to the point at which the midline crosses the aortic arch (Fig. 1).

The longer the ascending aorta the smaller this angle V will be. In normal hearts, Chinese or foreign, the angle V was usually found

to be between 24 and 28 degrees. Hearts with an angle of 20 degrees or less give the impression of being unusually erect. In this study 32 men and 15 women were found to have angles between 6 and 19½ degrees.

The angle h between the longitudinal axis of the heart and the long axis of the body was in close agreement with Kreuzfuchs'[1] average of 48 degrees in women and 52 degrees in men.

Van Zwaluwenberg and Warren's[29] auriculoventricular ratio expressed as A–V index $= \frac{\text{D O}}{\text{O G}^1}$ measured in terms of their longitudinal diameters in the roentgenogram was often found to be high in our series.

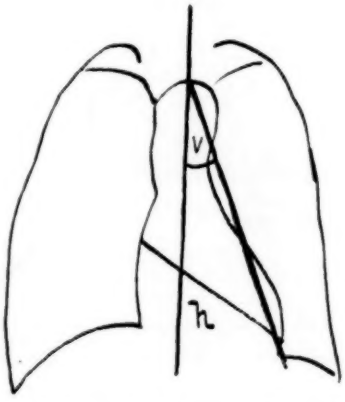

FIG. 1.—Angle expressing "verticality" of heart.

A high index is found in hearts with large auricular areas, for example, in mitral stenosis, and in individuals of asthenic build whose hearts often show the so-called mitral configuration in the roentgenogram.

About half of the subjects, males and females, examined, showed a high A–V index, as seen in Chart I and Table II.

Chart II illustrates the frequent coincidence of a high morphologic index with a mitral configuration of the heart. The possible error in measuring the distances D O and O G¹ in Fig. 2 is slight as the line G D¹ approximately corresponding to the auriculoventricular groove was drawn after examination by all three methods in common use. But since these measurements are derived from a photograph taken in frontal plane only it is realized that the position of the longitudinal cardiac axis should be taken into consideration. Rotation of this axis toward the sagittal plane, as it may occur for instance in a deep but narrow thorax, would produce a smaller and narrower cardiac shadow and may alter the auriculoventricular ratio.

A number of authors, among them Vaquez and Bordet, have considered this point and have advocated roentgenologic examination in both oblique diameters. Danzer,[5] Martinet[16] Moritz[19] and others have demonstrated the relationship of heart measurements to the dimensions of the thorax. Morphologic characteristics of the Chinese will have to be taken into account before a standard for them can be established. For the time however, a comparison of our measurements with those obtained on Europeans and Americans by the same standard laboratory methods[32] was the chief object.

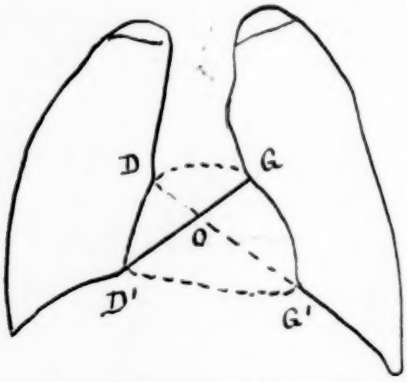

FIG. 2.—Auriculoventricular ratio.

Taken from Vaquez and Bordet:[30] The Heart and the Aorta

$\frac{D\,O}{O\,G^1}$ normally 0.53 to 0.70.

Below there is a summary of Charts I and II, showing the prevalence of longilinear build and the high incidence of mitral configuration. Both qualities are slightly more pronounced in women than in men.

TABLE II.—CORRELATION OF HABITUS WITH AURICULOVENTRICULAR RATIO.

No.	Habitus.	Ratio D O : O G1. Low.	Normal.	High.
	Males.			
1	Brevilinear	1		
10	Mediolinear	1	6	3
94	Longilinear	4	45	45
105	*Total males*	6	51	48
	Females.			
0	Brevilinear.			
2	Mediolinear	..	..	2
43	Longilinear	2	19	22
45	*Total females*	2	19	24
150	*Both sexes*	8	70	72

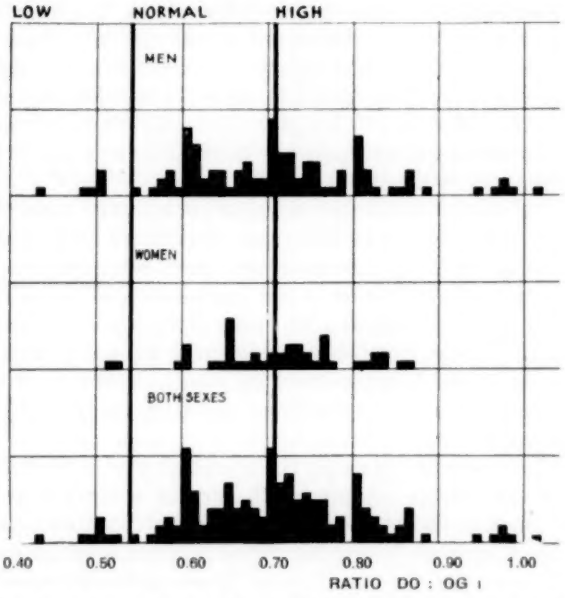

CHART I.—Auriculoventricular ratios in Chinese. The auriculoventricular ratios (D O : O G_1) are indicated by the black squares. The heavy lines enclose the normal range (0.53 to 0.70). Note the prevalence of high ratios.

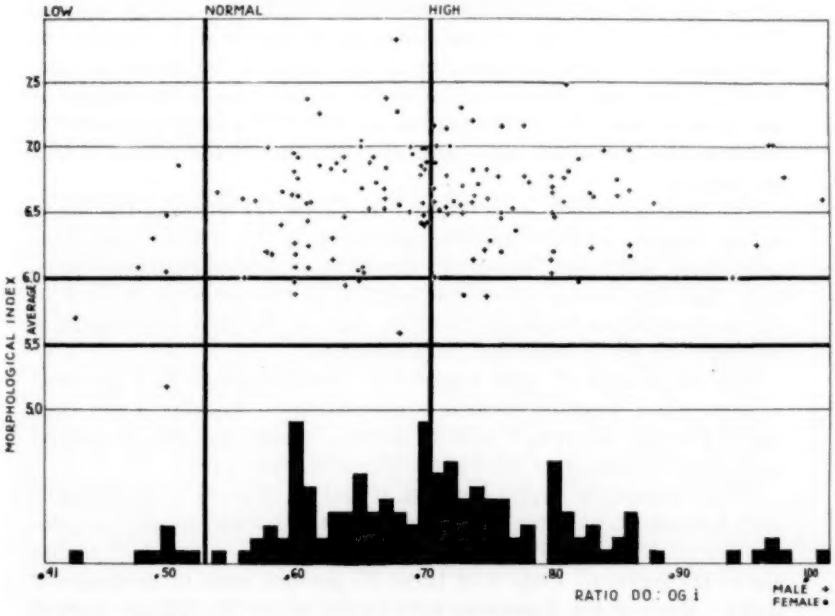

CHART II.—Correlation of morphologic index with auriculoventricular ratio. The auriculoventricular ratios are indicated by the black squares at the bottom of the chart. The morphologic indices by crosses and points. The heavy lines enclose the normal ranges. A–V = ratio : 0.53 to 0.70· M.I. : 5.5 to 6.

Electrocardiograms. The hypertrophy of the left auricle and of the right ventricle characteristic of mitral stenosis often finds an expression in the electrocardiogram. Notching or enlargement of the *P* wave in both directions and right ventricular preponderance are frequently recorded. Right ventricular preponderance can, however, be produced by a number of other factors and is therefore not pathognomonic of mitral stenosis.

Kraus and Nicolai[13] have for example commented upon the occurrence of S_1 in the electrocardiograms of children and of persons of asthenic build. The two authors demonstrated experimentally, in collaboration with E. Meyer,[14] the appearance of S_1 as the result of measures which produced a lowering of the blood pressure.

Meek and Wilson,[17] experimenting on dogs, have demonstrated that rotation of the heart around its longitudinal axis is more apt to produce deviation of the electrical axis than cardiac displacement to the right or left.

Stoss[26] has recently reported the correlation of different types of the initial ventricular complex with certain anthropologic characteristics. As this, the *Q–R–S* complex, usually contains the highest peaks in the electrocardiographic curve, it also is used for determination of the electrical axis, and Stoss' types represent merely a scale of electrocardiograms with various angles of the electrical axis, which may be useful for quick orientation.

None of the electrocardiograms of the 150 health subjects of this series showed any important departure from the normal curve. Two of them showed a slight widening of the *Q–R–S* complex to 0.08 seconds. The determination of the angle of the electrical axis, that is to say the direction of potential at the time of the height of the *R* wave, was done by Dieuaide's method.[7] This angle is included between the line which represents the direction of the potential and the horizon.

The findings which were entered on Chart III showing the angle on the abscissa and the morphologic index on the ordinate conform, as a whole, with Stoss' observation which, expressed in other words, tells that the normal electrocardiogram of the asthenic individual shows generally a tendency to right, that of the stenic individual a tendency to left ventricular preponderance.

The occurrence of right ventricular preponderance in 4 per cent of apparently healthy persons is noteworthy. Another 4 per cent showed angles between 0 and 30 degrees, which may be considered as a slight tendency to left ventricular preponderance.

While accepting angles between 0 and 90 degrees in accordance with Greene and Carter's statement[7] as the normal range, the prevalence of large angles is striking; 97 out 150 persons had angles above 60 degrees. Only 6 of these 97 persons were of mediolinear build. Each of the 6 persons with angles above 90 degrees showed

the so-called mitral configuration of the heart with high auriculoventricular index (between, 0.74 and 0.94) by teleoroentgenogram.

Comment. The etiologic history of Chinese patients with mitral stenosis of the rheumatic type conforms mostly to that of cases observed in central Europe, but the comparatively slight involvement of the joints in contrast to the severe cardiac damage resembles the course of the disease in young children. Meleney and Kellers discuss among other points the possible influence of the vegetarian diet of the Chinese upon their susceptibility for arthritis.

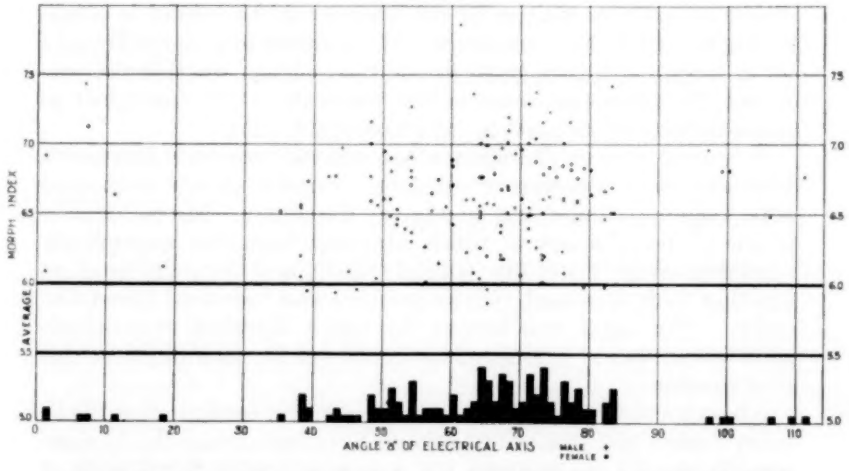

CHART III.—Correlation of morphologic index with angle of the electrical axis. The angles of the electrical axis are indicated by the black squares at the bottom of the chart, the morphologic indices by crosses and points. The heavy lines enclose the normal range of the M.I. : 5.5 to 6.

Hammond and Hsia Sheng[10] and Holt and Hammond* found the incidence of dental cavities among Chinese orphans to be about 10 times lower than among a similar group of American school children in Peking. This observation fully conforms with the findings on routine health examinations of the students and nurses of this college.† The lower incidence of foci of infection at an age which usually coincides with the most active period of rheumatic fever may have some bearing upon its manifestations. The high incidence of hemoptysis, similar to that observed in Durozier's disease, points to the presence of other peculiar factors, for instance, in the pulmonary circulation, as a counterpart to the relative hypotension observed among Chinese.[28]

The various measurements on normal persons made in these studies serve merely as mathematical expressions of different types

* Personal communication by J. W. Hammond.

† Personal communication by B. G. Anderson, D.D.S.

of build, cardiac outline, and electrocardiogram. These types are easily recognizable by inspection which in this way acts as a control against gross errors.

The features characteristic of Kraus' heart of the narrow chested, namely, a long, narrow heart, in median, vertical position with a long aorta, mitral configuration, and a large angle of the electrical axis, viz., tendency to right ventricular preponderance, were rarely encountered in their totality in any single subject. The majority of the hearts examined presented, however, one or several of these characteristics. Study of measurements of the various thoracic diameters and the position of the heart would be helpful in establishing standards for comparison. Mensuration of Chinese brought up in foreign countries could decide the question whether the prevalent characteristics found in this series should be considered as racial traits or be ascribed to environmental factors.

In several respects the observations recorded resemble Martinet's hyposphyxia, a circulatory symptom complex closely connected with longilinear build and circulatory dystrophy. Mitral stenosis is one of the diseases in which Martinet finds the hyposphyxic syndrome consisting of low arterial systolic and low pulse pressure together with increased venous pressure and increased blood viscosity. The latter two factors, for which Martinet recommends specific methods of examinations, could not be determined in this investigation.

Attempts to distinguish between mere mitral configuration of the heart shadow and true mitral stenosis have been based chiefly upon visualization of the enlarged left auricle in profile [60,25,31] with or without contrast filling of the esophagus. The number of complete observations including autopsy is as yet too small to permit a definite evaluation of these methods in differential diagnosis.

Extensive studies of the anatomy and physiology of the Chinese have begun to prepare the ground for a conception of endogenous factors in the causation of their diseases. The present investigations have attempted to present some problems of cardiac diagnosis from this viewpoint.

Conclusion. 1. The clinical picture of mitral stenosis among Chinese as obtained from a survey of 157 hospital records presents several prominent features commonly found in groups of patients, among which asthenic habitus is prevalent.

2. On examination of 150 healthy young Chinese adults a correlation could be demonstrated between three predominating characteristics, namely, asthenic build, mitral configuration of the heart, and a large angle of the electrical axis. A description of the patient's habitus, more exact and uniform than commonly used, might therefore help to evaluate the other findings in the individual case. Among the various anthropometric methods the determination of the morphologic index recommends itself by its simplicity.

3. In view of the fact that healthy persons of asthenic build often present the same type of cardiac outline and electrocardiogram as patients with mitral stenosis; and further as mitral stenosis seems to occur more frequently in persons of asthenic build, the diagnosis of doubtful cases should depend almost entirely on clinical evidence.

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ALLERGIC MIGRAINE.

Based on the Study of Fifty-five Cases.

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The migraine syndrome is a snag over which medical investigators have stumbled during the centuries past. Some of the early writers of the nineteenth century noticed a similarity between asthma, hay fever, and migraine. Vaughan[1] reported a series of cases from which it appears that migraine of all ages is often associated with a specific sensitization to one or more food proteins. His patients obtained entire or partial relief by eliminating from their diets the foods to which they were specifically sensitive. It is now generally accepted that the exciting factor in all seasonal hay fever, and practically all cases of asthma, is a sensitization to foreign proteins. One of us[2] in a recent work on the hereditary factor in allergic diseases, showed that migraine is interchangeable in the linkage with hay fever and asthma, which is good evidence that asthma, hay fever, and migraine, have a common etiologic factor. A study of the migraine problem from the standpoint of allergy during the past few years has certainly thrown new light on the subject. From a review of a series of cases studied by us during the last two years it appears that practically all cases of true migraine have as an exciting factor a sensitization to foreign protein, and that our treatment based on the allergic findings has given results equal to those in practically any other chronic disease. Henceforth

we believe the migraine symptom complex must be considered either curable or at least controllable in the majority of cases.

The material for this study is based on 55 cases of migraine whose ages range from six to sixty-eight years. All were private cases, American born, and about 75 per cent have been under observation from six months to two years. There were 23 males (41.8 per cent) and 32 females (58.2 per cent). The onset of symptoms occurred in 16, or 29.1 per cent, during the first decade; in 15, or 27.3 per cent, during the second; in 14, or 25.4 per cent, during the third decade, and in 10, or 18.2 per cent, between the ages of thirty and forty-six years. A large per cent of the patients were made up of housewives, stenographers and professional men. Seven of the 55 cases were physicians.

TABLE I.—DISTRIBUTION OF AGE OF ONSET OF CLINICAL MANIFESTATION OF MIGRAINE IN PATIENTS OF ALL AGES, BASED ON 55 CASES.

Age of onset.	No. of cases.	Percentage.
First decade	16	29.1
Second decade	15	27.3
Third decade	14	25.4
Fourth decade	10	18.2

The Hereditary Factor in Migraine. Practically all investigators give heredity as the most potent factor in the production of migraine. It need not be assumed, as is frequently believed, that the hereditary factor must be migraine itself. It has been our experience that it is only one of a number of symptom complexes which are metamorphosed in passing from parent to offspring and arise in different forms in different members of a family. For example, five children in one family might be specifically sensitive to wheat. From such a sensitivity asthmatic symptoms might appear in the first child, eczema in the second, hay fever in the third, urticaria in the fourth, and migraine in the fifth. The mother of the children might have been a hay fever sufferer whose symptoms were due entirely to a sensitivity to Bermuda grass pollen, and her mother might have had asthma due to a sensitivity to cat hair. The type of sensitivity from which the antecedent suffers has no relation to the type the descendent may have. It must be remembered that we do not inherit from our parents or grandparents or anyone, so far as that is concerned. Our parents and we inherit from the same germ plasm and therefore the same plans and specifications are used in our makeup, which accounts for our having traits in common. We inherit germ cells whose chemical combination is similar. In the germ cells are determinors which decide whether or not we will have the ability to become specifically sensitive, but we do not inherit the specific allergic disease. With this ability we may become specifically sensitive to one or more food proteins and from that sensitivity develop migraine, but we do not inherit migraine itself.

In the series studied, a positive family history of allergy was elicited in 47, or 85.4 per cent. There was a family history of migraine in 25, or 45.4 per cent. In 37, or 67.3 per cent, of the cases, there were other manifestations of allergy. In other words, individuals born with the ability to become specifically sensitive to food protein and have migraine, should also under adequate contact become sensitive to inhalants and have asthma or hay fever, and from the above figures apparently they do.

Exciting Factors. From a study of the hereditary factor in migraine it seems logical to believe that the exciting factor is always a specific sensitivity to one or more foreign proteins. In every case studied a positive reaction to one or more foreign proteins, either food or inhalants, was found. By no means, however, did we feel that we found the chief offending protein in every case. The following table will show the positive food findings:

TABLE II.—OCCURRENCE OF SCRATCH AND INTRADERMAL REACTIONS TO THE MOST COMMON PROTEINS USED IN TESTING 55 CASES OF MIGRAINE.

Food reactions.	No. of cases.	Percentage of positive reactions.	Food reactions	No. of cases.	Percentage of positive reactions.
Wheat	38	69.0	Tea	10	18.1
Milk	25	45.4	Mushroom	9	16.3
Egg	20	36.3	Peach	9	16.3
Fish	36	65.4	Lemon	9	16.3
Bean	33	60.0	Sweet potato	8	14.5
Nuts	23	41.8	Artichoke	8	14.5
Turnip	21	38.1	Beet	8	14.5
Cheese	19	34.5	Apricot	8	14.5
Radish	17	30.9	Grapefruit	8	14.5
Parsnip	17	30.9	Irish potato	7	12.7
Eggplant	17	30.9	Fig	7	12.7
Barley	15	27.2	Orange	7	12.7
Asparagus	15	27.2	Garlic	7	12.7
Lettuce	15	27.2	Vanilla	7	12.7
Cabbage	13	23.6	Paprika	7	12.7
Buckwheat	12	21.8			
Rye	12	21.8	*Inhalants*		
Pea	12	21.8	Feathers	34	61.8
Celery	11	20.0	Dog hair	20	36.3
Cottonseed	11	20.0	Cat hair	17	30.9
Cauliflower	11	20.0	Horse hair	16	29.0
Cantaloupe	11	20.0	Cattle hair	11	20.0
Coffee	11	20.0	Rabbit hair	9	16.3
Spinach	10	18.1	Wool	9	16.3
Onion	10	18.1	Orris root	14	25.4
Tomato	10	18.1	Pollen	31	56.3

Most patients were found sensitive to a number of foods, but dietary manipulation proved in the majority of cases that one or two of the foods would be the chief offenders. Wheat was positive in 38 cases and was considered a very important factor in 14. Milk was definitely positive in 25, and was strikingly important in 6. Eggs were positive in 20, and played a very important part in 4.

Fish was positive in 36 cases; bean in 33; nuts in 23; lettuce in 15; celery in 11, and so forth. From our study it appears that the average case of migraine is sensitive to a multiplicity of food protein, and many to inhalants. This is not unlike the adult asthmatic, who is usually sensitive to a large number of foreign proteins.

Predisposing Factors. Conditions which play a part as predisposing factors are as follows: (1) Physical fatigue; (2) mental fatigue and depressed states; (3) thyroid disfunction; (4) genitosexual cause; (5) toxic states; (6) disturbance of the special senses.

We have observed a number of patients who developed typical attacks of migraine following exhaustive physical exercise. It is very common to have the attacks follow mental strain, prolonged worry, or extreme excitement. The headaches may come on periodically with the menses or be precipitated by psychosexual excitement. Endogenous toxins, such as from infected teeth, tonsils, or toxins from an exogenous source, such as lead poisoning, or partially burned gas fumes, may bring on the headache. Refractive errors, or a disturbance of the normal hearing, smelling, seeing, or tasting, may play a part in precipitating an attack. In the opinion of the authors the above factors mentioned must be considered as predisposing factors only, just as we would consider cold air, exertion, excitement, infection in the bronchial tubes and other parts of the body, and chemical odors, as predisposing factors and not the exciting one in true bronchial asthma.

Symptomatology. The migraine attack may follow severe physical exhaustion or prolonged mental strain or worry, or extreme excitement. Such attacks, therefore, may come anytime during the day, usually without prodromal symptoms. Frequently, without any known cause, however, severe attacks of migraine may occur following a restful, sound sleep. A patient commonly wakens with a feeling of "goneness" and feels "draggy" until the latter part of the morning, when nausea and headache appear. In about one-third of our cases a feeling of nausea or abdominal discomfort was not present. In the remaining cases, however, either nausea, mild or severe, associated with vomiting, slight or marked, at some time during the attack occurred. As a rule the headache manifested itself as a sensation of mild pressure, frequently in one or both temple regions. The pressure disturbance gradually increased in area and intensity to the extent that many patients declared that they felt that the top of their skull would come off. Most patients reported that when the severity of the pain reached its peak there was no one part of the head in which the pain seemed more severe than another. Only in 9 per cent of the cases was the symptom of zigzag lights present. The severity of attacks in one patient may vary greatly from time to time, and of course the severity in different patients, like in asthma or hay fever, varies greatly. Many suffer from pain, nervousness and exhaustion to the extent that they are

confined to their beds during a small part or most of the time the attack is on. The duration of their attacks averaged two days. Many reported light attacks of only a few hours, and other attacks lasting four to five days. The frequency of their attacks occurred from a few days to a year, the average being fifteen days. Some patients reported that they were never free from a dull headache between the paroxysms of attacks.

A brief review of the following cases seems justified, as from them will be illustrated many points previously discussed and that will be subsequently mentioned.

Case Reports. CASE I.—M. A. B., a man aged forty-five years, had suffered from very severe attacks of migraine since eleven or twelve years of age. During the past eighteen years his attacks occurred on the average of every two weeks, and lasted from two to three days. The severity of his attacks was such that at least one day during the period he was unable to work.

He had one maternal uncle with asthma; the maternal grandfather with asthma, and the mother had eczema. During his early life he had hives on a number of occasions, but except for his migraine he has never consulted a physician since a small child.

He is a stove manufacturer and lives a very busy life and one that requires a great deal of mental strain. It was interesting to have him tell how his headaches had interfered with his work. He said, for example, that he would have an appointment with a wholesale house to discuss the subject of the sale of his product, and by the time his appointment would occur he would frequently be in bed with a severe headache.

Scratch and intradermal methods of testing revealed the following: milk ++; cheese +; codfish +; crab ++; salmon +.

An outline concerning his diet was given him, in which there were excluded from the diet milk and all milk products, and all shell sea foods, but no other foods. This man was first seen two years ago, and since that time he has had but one attack except on two occasions when he was at the seashore and ate heavily of sea foods, and reported rather severe typical migraine attacks.

This case illustrates a type of migraine in a business man who has had his business very seriously interfered with by the severity of the attacks. This is not an unusual case. It also illustrates the effect of anxiety and mental strain. He is sure, as he states from trying it out, that taking the offending foods will bring on attacks and that when he leaves them out of his diet his work may be very heavy and there may be considerable mental strain, but he will remain free from migraine attacks.

CASE II.—Mrs. W. T. C., housewife, aged thirty-four years, had suffered from seasonal hay fever nine years, migraine since in the teens, and a severe colitis for fifteen years. She was a very nervous patient. She had been under the care of a number of physicians, including the neuropsychiatrist, the gastro-enterologist, and the rhinologist, but had found little relief. Her attacks of migraine were only moderately severe at times, but were quite frequent. At other times they were very severe and there were present many of the signs which occur in true migraine, namely, severe headache, nausea, vomiting, zigzag lights, marked prostration.

Scratch and intradermal testing revealed a positive reaction to a large number of foods, the chief of which were eggs, buckwheat, beans, celery and cantaloupe, and a marked reaction to ragweed and a number of the grasses.

The positive foods were eliminated from her diet with a result of practically complete freedom from the migraine and complete freedom from colitis. She is being desensitized at present against the ragweed as a means of preventing her seasonal hay fever.

This case illustrates one who has three manifestations of allergy, namely, hay fever, mucous colitis, and migraine. It is quite possible that the chief etiologic factors in her migraine and mucous colitis are the same. Her hay fever is seasonal in type and the chief factor is pollen. However, it would be folly to treat this individual for her hay fever without eliminating the foods to which she is specifically sensitive and which are causing the other allergic manifestations. She has learned that partaking of the forbidden foods will bring on attacks and leaving them off will give her freedom.

Case III.—A. W. H., merchant, aged thirty-eight years, came to our Clinic with a history of recurrent attacks of severe headache, which started in childhood. His maternal grandfather had migraine. He was told that he could not take milk and remain free from headaches. The patient's past history was entirely negative from the standpoint of disease except for headaches. His trouble first began as a very small child, disappearing around twelve but recurring again at twenty-two. The attacks are from three to four days' duration and occur about once a month. The pain is very severe over one eye only. It is stabbing in character and apparently goes through to the other side of the head. He has learned that extra work, especially mental strain, will help to precipitate an attack.

Very careful food testing revealed a sensitivity to milk only. Milk was removed from his diet, with complete relief except for one or two times that he has taken less than a teaspoonful of milk just to try it out and has found this sufficient to bring on a headache attack.

Most patients who have migraine are sensitive to a multiplicity of proteins. This man, differing from the rule, however, was found sensitive only to milk.

Case IV.—K. W., a physician, aged thirty-eight years, developed severe attacks of migraine at the age of thirty-six. His attacks were very severe and he had all of the symptoms which occur in migraine. He had noticed a number of foods which he was sure helped in provoking an attack. He has hay fever and some asthma. His maternal grandmother had migraine, his father had mucous colitis.

On testing him we found him extremely sensitive to a very large number of foods, including the following: Wheat and its split products +++; coffee ++; bean +++; kidney bean ++++; turnip ++++; asparagus ++; celery ++++; tomato ++; garlic +++; peach ++++; orange +++; grapefruit ++; pineapple +++; lobster ++; clam ++; crab ++; almond ++; peanut ++++; hickory nut ++++; vanilla ++; parsnip +++; ginger ++++.

A careful elimination of the foods to which he is specifically sensitive has given this physician freedom from attacks during the last eight months, except for two. One followed a lawsuit, during which there was a great deal

of excitement and mental strain, and the other following a hunting trip, during which time he was physically exhausted and had eaten some wheat bread.

This case illustrates the effect of the predisposing factor, such as mental strain and physical exhaustion, and also the effect of the exciting factor, such as the eating of the specific foods to which he is sensitive. It is interesting to note that his trouble started in the third decade. From our findings it appeared that about an equal number developed symptoms in the first, second, third and fourth decades.

CASE V.—Mrs. W. R. B., housewife, aged thirty-one years, gave a history of migraine since she was thirteen years of age and hives at intervals since a small child. She had one brother with hay fever; one sister with hay fever; her mother had migraine; her maternal grandfather had migraine, and her father had hives. She gave a history that her migraine occasionally would occur during the intramenstrual period but usually would occur just previous to the menses and would commonly be so severe, along with her menstrual period, to require her to remain in bed during a large portion of the period.

Food testing gave a reaction to the following proteins: Casein ++; coffee +; blackeyed pea ++; pork +; raspberry +++; wheat ++.

Elimination of the offending proteins has given this patient entire freedom from her trouble.

This patient illustrates the type who have their attack of migraine frequently coincident with the menstrual period or occurring just before. This is not unusual. The nervousness near the menstrual period is not the exciting factor but the predisposing cause. When the exciting factor is eliminated, as was done in her case, namely, the elimination of the foods to which she is specifically sensitive, the nervousness of the menstrual period produced no headache.

Discussion. In all the cases presented, and as has been previously mentioned, in a large per cent that we have studied, there is a definite hereditary history of migraine or other allergic manifestation, namely, asthma, hay fever, eczema, urticaria, and chronic colitis. Of the 5 cases presented, which are typical of the majority studied, the predisposing factors, such as those previously mentioned in the article, seem to play a definite part in bringing on the attacks of headaches, but these 5 patients, along with a majority of the others studied, reported that when they adhered strictly to their diet they were free from headaches in spite of physical exhaustion, mental strain, menstrual periods, and the like. In allergy this parallels Koch's postulates as applied to bacteriology and is a very necessary antecedent to the acceptance of the theory as to the exciting factor.

General Health and Mental Activity of Migraine Patients. In our study of migraine patients we have been impressed with the fact that their general health is usually above the average. The syn-

drome occurs more commonly in a class of people whose vegetative nervous system is highly developed, most of whom are very active mentally. The symptom complex is not commonly found in the negro, Indian, or among the Chinese. In these races allied allergic manifestations, namely, hay fever, asthma, urticaria, and certain forms of eczema and colitis, are comparatively infrequent.

Methods of Testing for Exciting Factors. The scratch method of testing should first be used. All questionable reactions should be checked by the intradermal method. If only the scratch method is used, many proteins to which the patient is specifically sensitive will not be found. Treatment outlined on such findings therefore would not give results. An immediate reading should always be made, but also a four and a twenty-four-hour reading should be made, since delayed reactions are common. Food reactions in migraine, like those in eczema and urticaria, are difficult to read. One must always take into consideration the variable reactivity of different skins.

Multiple sensitivity is the rule. All patients except one in our series were found sensitive to more than one protein. Such a finding is true in other allergic syndromes. Multiple sensitivity should be the rule, since an individual born with the ability to become sensitive to one food protein naturally should become sensitive to others, especially if they have partaken of them in large amounts.

Differential Diagnosis. Migraine must be differentiated from functional headaches, trifacial neuralgia, myalgia, ordinary intoxication and infections, such as those of alcohol, tobacco and uremia, and from headaches due to pituitary disfunction. A clear-cut history of periodic headaches over a long period of time, with freedom between, and especially with a history of the usual prodromal symptoms spells migraine. In those cases in which the onset has been recent of course the differential diagnosis is a little more difficult. In making a differential diagnosis a familial history of allergic diseases should be given much weight, that is, if the headache is somewhat an atypical one and the familial history is great, one should be careful in not diagnosing the headache as a migraine one, while on the other hand if the symptoms are not clear cut and the family history is negative so far as allergic diseases are concerned, one should be careful in calling the headache migraine in type.

Prognosis. It is generally taught that migraine of all types gradually disappears in the third and fourth decades and that there are only few exceptions to this rule. From our study this appears not to be true, since of the 55 cases 7, or 12.7 per cent, came seeking relief during their sixth decade. From the standpoint of life and death, and also complications, prognosis of course is good. The complications that occur in many are those of other allergic manifestations, especially eczema, asthma and hay fever.

Treatment. Until relatively recent times migraine was placed by the medical profession in the category of uncontrollable human ailments. As many remedies as there are drugs in the pharmacopeia have been suggested for it but their efficacy is in inverse proportion to their number. Until the last decade much attention was given to the predisposing factors but too little attention has been paid to the exciting causes. This was likewise true of the other allergic syndromes. However, since the recent discovery of exact means of determining the exciting factors in each case more attention to the disease is being given by the medical profession.

It is obvious, in the first place, that the predisposing factors should be eliminated. For example, plenty of rest and sleep should be taken by the sufferer. Avoidance of physical exhaustion, mental fatigue and worry is always in order. Toxic states should be sought for and eliminated if found. Correction of refractive errors and any errors of the other special senses should be done.

When all the foregoing measures have been taken many patients will be somewhat better, but the vast majority will continue to have their migraine. Not until the exciting factor, namely, the foods to which they are specifically sensitive, is removed from their diet, can one hope for good results. All of the foods to which a patient is found definitely sensitive should be removed from the diet. In some cases it is impossible to find them by testing, or at least all of them. In such patients eliminative diets, based on our knowledge of the most common food factors in other cases, are used. Other foods are added or subtracted from time to time as a means of determining the offending food.

In our series of 55 cases, 29, or 52.7 per cent, obtained from 85 to 100 per cent freedom from symptoms, which we consider excellent results. There were 10, or 18.2 per cent, who received more than 60 per cent relief, which we classify as good results. Another 11, or 20 per cent, received more than 40 per cent relief, which we considered fair results. In 5 cases were we able to give less than 40 per cent or no relief, which we considered poor results.

From our findings it appears that the results in the treatment of migraine are as good or better than those obtained in nearly any other chronic disease. The average migraine patient who receives more than 80 per cent results, practically speaking is well so far as the symptoms interfering seriously with his comfort or his carrying on a gainful occupation is concerned. Those cases who receive more than 60 per cent relief frequently are changed from very uncomfortable people, unable to carry on a gainful occupation, to comfortable, practical individuals. Even those who received 40 per cent relief were grateful patients. From our findings we are led to believe that the exciting factor in migraine is a specific sensitivity to food, which can be found in the majority of cases, and the treatment based on such findings gives results that are well worth while.

Summary. 1. A family history of allergy was elicited in 85.4 per cent of the cases.

2. From a study of the hereditary factor in migraine it appears that it is interchangeable in the linkage with asthma and hay fever, which is good evidence that these syndromes have a common etiology, namely, a specific sensitization.

3. The exciting factor in migraine is probably always a specific sensitivity to one or more foreign proteins.

4. There are many predisposing factors, such as (*a*) physical fatigue; (*b*) mental fatigue and depressed states; (*c*) thyroid disfunction; (*d*) genitosexual cause; (*e*) toxic states; (*f*) disturbance of the special senses.

5. The onset of symptoms occurred in nearly one-third of the cases during the first decade.

6. The persistence of migraine symptoms up until and through the sixth decade is not uncommon.

7. Migraine patients are usually above the average both mentally and physically.

8. Treatment should consist of thorough elimination of the foods and dusts to which the patient is found specifically sensitive.

9. Results in the treatment of migraine are as good or better than those obtained in nearly any other chronic disease.

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MULTIPLE ANEURYSMS OF THE ARTERIES OF THE RIGHT ARM ASSOCIATED WITH ARTERIOVENOUS FISTULA AND ARTERIAL EMBOLISM.

REPORT OF A CASE.*

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The association of multiple arterial aneurysms in an extremity with arteriovenous fistula and arterial embolism is rare. The case herein reported is of a patient who presented aneurysms of the brachial, radial, superficial palmar, common volar digital and volar digital arteries of the right arm, and also embolism of the radial

* Work done under the direction of Dr. G. E. Brown, Division of Medicine, The Mayo Clinic.

artery and an arteriovenous fistula of the hand. The interest in such a combination of changes is no less intense from a pathologic standpoint than that aroused clinically because of the wide range of physiologic studies possible. Of equal interest are the therapeutic problems raised by such a group of anomalies.

Aneurysms of the arteries of the upper extremities are uncommon and usually traumatic in origin. Holt, in a review of the literature up to 1882, found only 14 cases of brachial aneurysm due to disease. Lyle, in 1924, in an exhaustive review of the literature, was able to collect data on 61 published cases of aneurysms of the palmar arches and added one case of his own. Of these, 2 cases only were spontaneous; the remainder were chiefly traumatic in origin and therefore affecting the superficial palmar arch (54 cases) more frequently than the deep arch. Pemberton, in a review of the cases in which an aneurysm was treated surgically in The Mayo Clinic from January, 1915, to April, 1926, reported a total of 41 cases of arterial and arteriovenous aneurysm. Twenty-five of these were arteriovenous, 16 were acquired, and 9 were congenital. Reid,[16] in a study of 33 cases of arteriovenous fistula, disclosed two present in the hand. These were both the result of trauma. He included in this group 6 congenital cases which were chiefly of the cirsoid aneurysm type. The small number reported indicates that the lesions are rare.

From the pathologic standpoint, the etiology of such aneurysms in the absence of trauma and syphilis and the development of congenital arteriovenous communications is interesting. Multiple aneurysms may develop in different arteries of the body, as in the case recorded by Kolodny, in which there were aneurysms of the right popliteal, right axillary, left carotid, right external iliac arteries and the descending thoracic aorta. On the other hand, they may be multiple and localized to one peripheral vessel, such as in the case reported by Skillern, in which there were two small aneurysms in the brachial artery. It is well known, of course, that multiple aneurysms of the aorta and cerebral vessels are not uncommon. It is interesting to speculate whether or not multiple aneurysms in one vessel may be due to the effects of trauma or to other influences on an artery which already constitutes a place of lowered resistance. The question of the exact mode of development of arteriovenous fistula, cirsoid aneurysm and other abnormal arteriovenous communications is still unsettled. The belief at present is that these communications are either developmental anomalies in which capillaries are not formed so that the artery and vein communicate directly, or that they are neoplastic in origin.

Physiologic studies of arteriovenous fistulas are unusually interesting from the standpoint of the local and general effects produced. Among the former may be included changes in surface temperature of the affected part, the marked development of neighboring col-

lateral circulation, the changes in the length of the extremity in certain cases, and dilatation of the proximal artery and the veins. Brown and Pemberton called attention to the high oxygen content of the blood of the regional veins and to its pathognomonic significance in the diagnosis of arteriovenous fistula. The general effects on the cardiovascular system have been particularly emphasized by Holman. As he has pointed out, the changes produced depend primarily on the size of the fistula and on an unobstructed return flow to the heart. The changes produced include lowering of systemic blood pressure, elevation of pulse rate, increase in blood volume, and dilatation and hypertrophy of the heart, besides other changes.

TABLE I.—MEASUREMENTS OF LENGTH AND CIRCUMFERENCE OF BOTH ARMS.

	Right, cm.	Left, cm.
Circumference:		
Midarm above aneurysm	23.7	23.7
Level of aneurysm	26.4	22.7
Midforearm	24.0	24.7
Wrist	16.5	16.0
Base of index finger	9.5	8.0
Length:		
Distal end of clavicle to tip of middle finger	84.5	81.0
Tip of olecranon to tip of middle finger	52.0	49.0
Distal crease of wrist to tip of middle finger	19.0	19.0

Because of the great interest which the following case aroused clinically and because of the physiologic and pathologic studies made, it was considered to be worth reporting.

Report of Case. The patient, a farmer, aged forty-three years, registered at the Clinic February 13, 1929, for treatment of an aneurysm of the right brachial artery which had developed gradually over a period of fourteen years without apparent cause. The past medical history was essentially negative and the patient denied syphilitic infection. The right arm was not disabled until December, 1928, when he experienced a sudden sharp agonizing pain just above the wrist in the right radial artery. The hand became blue and numb and morphine was required to relieve the pain. Since that time the right index finger and the surrounding palm had been somewhat blue and after careful questioning the patient remembered that he had always had a "hot spot" in the palm at the base of the index finger.

The general examination was essentially negative with the exception of the right arm. There was an expansile pulsating mass, approximately 5 cm. in diameter, just above the internal condyle of the humerus. The superficial veins of the forearm were distended and there was a soft swelling 2 cm. in diameter over the radial artery in the middle portion of the forearm. The pulsations of the radial artery were vigorous up to the wrist, where they suddenly ceased, and at this point the artery was exceedingly tender. The palm at the base of the index finger was cyanotic, spongy and soft, as was the index finger up to the proximal interphalangeal joint. The right forearm was 3 cm. longer than the left. Abnormal auscultatory sounds were not present. Significant changes in blood pressure in the right arm were absent and venous pressure was roughly equal in both forearms. Laboratory examinations were negative. A roentgenogram of the right hand was reported as showing an old fracture of the first phalanx of the fifth finger.

Special examinations disclosed definitely abnormal responses to changes in posture on the right with blanching of the fingers on elevation of the arm (180°), quick filling of the index finger and surrounding palm (purple) and slow filling of the remainder of the hand which remained pink with the arm at the side (0°). Compression of the palm at the base of the right index finger, which presumably obliterated the arteriovenous fistula, caused the pulse beat to drop almost immediately five to seven points on several occasions[8,12]. On fluoroscopic examination, it was found that the heart was of normal size and there was no change in size with postural changes of the right arm or obliteration of the fistula. On compression of the brachial

FIG. 1.—Right and left arms before operation; just above the right elbow is the swelling produced by the brachial aneurysm; the superficial veins on the right are more prominent, especially on the radial side; the fingers on the right are drawn toward the ulnar side.

artery above the aneurysm, color in the hand returned in two to three minutes; normally it would return almost immediately. The results of oxygen and temperature studies are shown in Tables II and III. Calorimetric studies of the hands preoperatively showed that elimination of heat in small calories in twenty minutes for the entire hand was, for the right hand, 260, and for the left, 130 (normal 110 to 130).

It was obvious that the patient had a right brachial aneurysm and an arteriovenous fistula of the right hand, as indicated by the warmth of the hand, the neighboring engorged veins, the calorimetric studies and the presence of almost pure arterial blood in the regional veins of the right hand.

Following adequate development of the collateral circulation of the right arm by the method advocated by Matas, the brachial aneurysm was surgically obliterated March 12, 1929, although it was realized that the presence of the arteriovenous fistula was a serious complicating factor. Return flow from the distal end of the brachial artery following ligation of the proximal end was satisfactory at the time of operation. Following operation, there was considerable pain in the right hand, which was partially relieved by the application of heat. Gradually the pain became more severe and the impression was gained that thrombosis of some of the vessels of the hand had occurred. Typhoid vaccine and radium chlorid intravenously[1] and heat were of no benefit in relieving the steady burning pain. The hand was

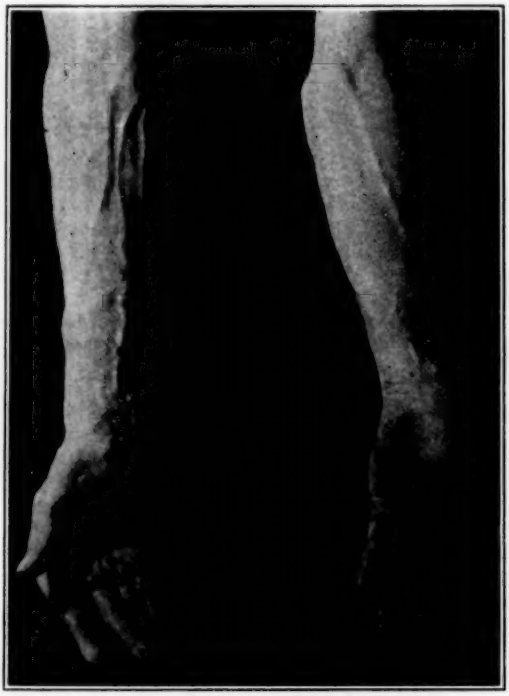


FIG. 2.—Right and left arm before operation; volar surface.

blue and cold except for the "hot spot" which was still warm, and motion was very much limited. It was obvious that the arterial blood supply to the hand was inadequate, but it did not seem wise to attack the arteriovenous fistula surgically because experience in previous similar cases had shown this to be a difficult, if not impossible, procedure to carry out successfully. It was finally necessary to amputate the forearm to relieve the pain. The patient's convalescence was uneventful.

The arterial system was injected with mercury (Horton's method). The course followed by the mercury can be seen in roentgenograms taken during various stages of the injection (Fig. 3). The mercury, under low pressure, entering the radial artery with the arm in the horizontal position passed through small anastomosing branches to the volar interosseous artery and

then on to the larger arteries of the palm. Within a few minutes the mercury was returning from a superficial branch of the cephalic vein. Fig. 3*a* shows that at this time none of the arteries of the fingers was filled with mercury, and the mercury was already returning from the vein. Slight increase in pressure produced injection of the vessels about the base of the index finger (Fig. 3*b*), but still mercury did not enter the finger tips. With further slight increase in pressure, the mercury finally entered the arteries of the fingers but it also filled most of the venous system of the hand (Fig. 3*c*).

TABLE II.—VENOUS OXYGEN STUDIES OF RIGHT HAND.

Blood.	Date.	Oxygen capacity, vol. per cent for each 100 cc.	Oxygen content, vol. per cent for each 100 cc.	Saturation, per cent.	Unsaturated blood, vol. per cent.	Unsaturation, per cent.
Vein of right arm near wrist	Feb. 18, 1929	17.7	15.6	88.2	2.08	11.8
Vein of right index finger	Mar. 30, 1929	18.5	17.0	91.0	1.50	9.0
Control vein of left arm	Mar. 30, 1929	..	12.5	52.0		
Normal arterial	....	21.0	20.0	95.0	1.00	5.0
Venous	....	21.0	14.0	70.0	7.00	30.0

TABLE III.—SURFACE TEMPERATURE STUDIES OF RIGHT AND LEFT HANDS: BEFORE AND AFTER OPERATION, DEGREES CENTIGRADE.

Four Weeks Before Operation.

Site.	Right.		Left.	
	Tip.	Second joint.	Tip.	Second joint.
Thumb (2 and 3)*	27.2	28.7	28.6	30.3
First finger (5 and 6)	28.6	30.6	27.7	29.5
Second finger (7 and 8)	25.4	30.5	28.4	29.4
Third finger (9 and 10)	25.7	29.1	29.3	29.7
Fourth finger (11 and 12)	25.1	28.2	29.6	29.5
Palm (4)	32.1		29.4	
Palm (13)	29.4		29.4	
Palm (15)	32.6		30.2	
Arms	30.9		30.9	

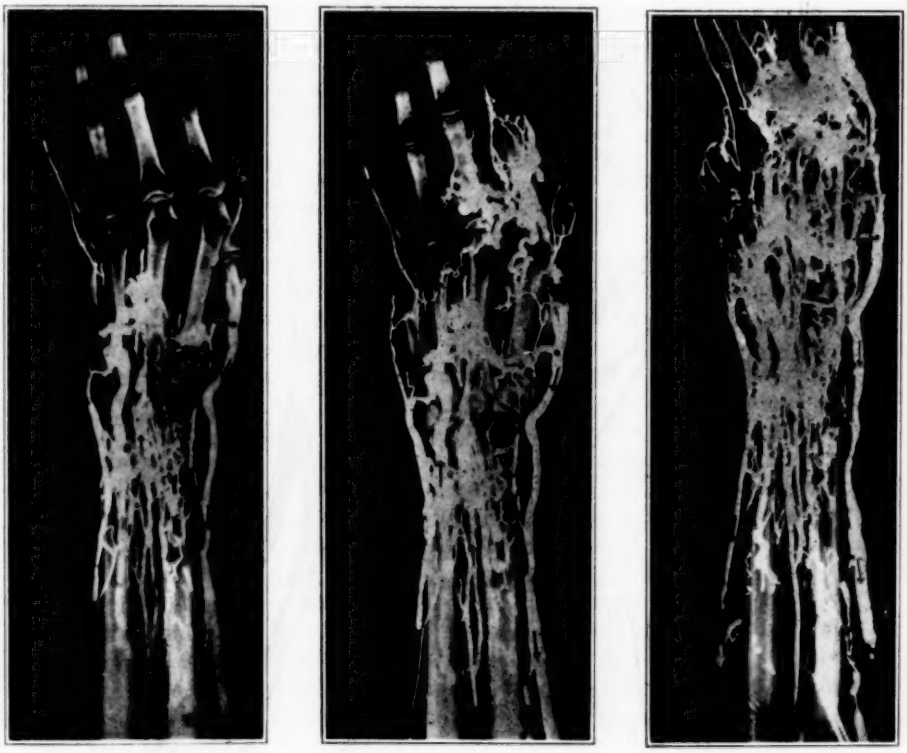
Two Weeks After Operation.

Site.	Right.	Left.
Palm (2)*	30.6	30.9
(15)	31.5	30.9
(14)	30.1	31.0
(4)	35.0	
Fingers (5)	31.4	
(6)	30.0	
(7)	28.6	31.2
(11)	28.5	30.3

Three and a Half Weeks After Operation.

Site.	Right.	Left.
Fingers (11)*	33.3	36.6
(9)	33.3	36.5
(7)	33.7	36.3
(6)	35.7	36.9
Distal palm (12)	34.9	36.0
(10)	36.4	37.2
(8)	36.9	37.2
(4)	35.0	36.3
(2)	34.0	36.3
Palm (1)	37.0	36.4
(15)	37.5	37.5
(13)	36.5	36.5
(14)	35.8	36.1
	37.0	36.3

* Numbers refer to points on hand shown in Fig. 4.



a *b* *c*

FIG. 3.—The vascular tree of the right forearm during injection with mercury following amputation (Horton's technique). The arrows indicate the direction of flow. The large shadow on the right is a superficial branch of the cephalic vein.

a.—Low pressure. Mercury was allowed to flow in the radial artery in the middle portion of the forearm (as shown by the arrow at bottom of photograph). It is obstructed after a short distance because of thrombosis in the vessel, and therefore, passes through small arteries over the radius to enter the volar interosseous artery (lying between the radius and ulna). Proceeding to the palm, it enters the palmar arteries and flows toward the base of the second metacarpal bone. It then passes into a superficial branch of the cephalic vein near the point indicated by the arrow and dot, and returns by the vein toward the heart.

b.—Slightly higher pressure than *a*. Flow the same as in *a*, but in addition the mercury fills the aneurysms and dilated vessels in the region of the proximal phalanges of the index and middle fingers; it may be noted that the arteries of the last three fingers are not filled with mercury.

c.—Slightly higher pressure than *b*. Flow same as in *b;* in addition, the mercury has finally entered the vessels of the fingers but at the same time nearly all of the venous channels contain mercury as well; the constancy of the communication at the site of the arrow and dot and the absence of mercury in the course of the radial artery may be noted.

Anatomic study of the vessels revealed small aneurysms of the radial, superficial, palmar, common volar digital and volar digital arteries, nearly all of which contained adherent and organized thrombi (Fig. 4). The radial

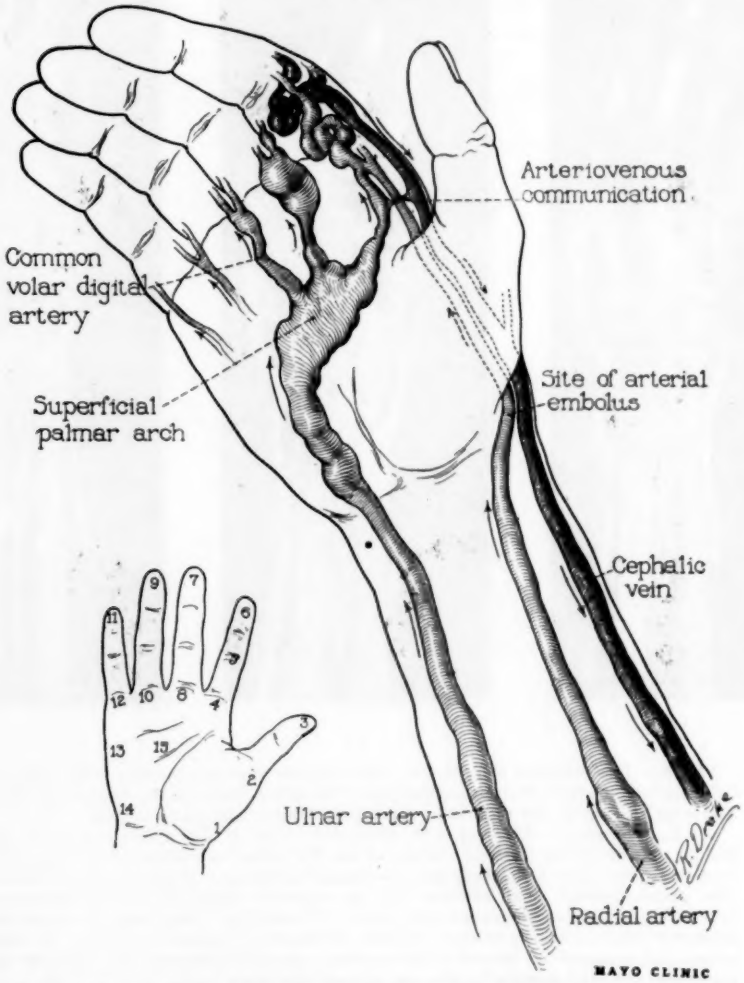


FIG. 4.—Large vessels of the right hand as determined by dissection. The chief points of interest are: (1) Dilatation of the radial and ulnar arteries; (2) small aneurysm of the radial artery; (3) narrowing of radial artery at site of embolism; (4) aneurysmal dilatation of the superficial palmar arch with absence of volar branches to the last two fingers; (5) aneurysm of the common volar digital artery to the index and middle fingers with aneurysm of the volar digital artery to the index finger; (6) tortuous veins surrounding base of index finger; (7) probable site of arteriovenous fistula; (8) prominent superficial cephalic vein.

artery above the wrist was dilated and tortuous, and at the wrist it was unusually small and completely obliterated. The superficial veins were dilated, especially those on the radial side of the forearm. A definite

arteriovenous communication was not found in careful dissection of the forearm and hand. A diagram of the condition in the vascular tree following dissection of the forearm is shown in Fig. 4.

The arterial walls throughout the forearm were abnormally sclerotic and presented fibrotic changes of the media and marked but irregular proliferation of the intima with excessive thinning in the areas of aneurysmal dilatation. The majority of the vessels contained organizing thrombi. There was slight evidence of an inflammatory process as indicated by perivascular lymphocytic collections. The veins carrying the arterial blood presented histologic pictures somewhat similar to those of arteries with hypertrophy of the elastic and muscular portions of the walls of these veins.

Comment. The cause of such extensive vascular disease of an extremity is uncertain. The absence of evidence of syphilis practically excludes this factor. The presence of a moderate number of perivascular lymphocytic collections and other histologic features in several of the sections was not inconsistent with the diagnosis of thrombo-angiitis obliterans, although not pathognomonic of this disease. It is possible, as suggested by Skillern, that aneurysms of this type are the result of some abnormal influence on arteries already a place of lessened resistance, or that the aneurysms developed in the arteries proximal to an arteriovenous fistula, as has been reported by Curtis, Osler and Da Costa. The absence of general systemic effects of the fistula make this seem unlikely. The conclusion is evident that the arterial changes were due to some defect in arterial development or to some abnormal sclerotic process in the walls of the vessels, although an infectious process cannot be absolutely excluded. The etiology of the arteriovenous fistula is uncertain also but several factors point to it as being congenital, that is, the history of a hot spot in the palm of the hand throughout life, the history of slow healing of a fractured phalanx ten years previously and the excessive length of the right forearm which must have occurred prior to the age of twenty years.

Anatomic preoperative studies showed the right forearm to be 3 cm. longer than the left. This is a common observation in the presence of an arteriovenous fistula before complete skeletal ossification has occurred and is the result of the presence of excessive arterial blood at the epiphyses. It seems probable that the arteriovenous fistula was in the palm somewhere near the base of the index finger (Fig. 4). This is borne out by the discoloration in this area, the bradycardia response to pressure over this point, and the escape of mercury into the veins in this region (Fig. 3), at low pressure during the injection by Horton's method following amputation. The fistula was evidently small and probably contained multiple openings. The microscopic data are significant in that the vessels showed a markedly abnormal sclerotic process, the exact nature of which is not certain. An infectious process could not be absolutely excluded. The thrombi present in the majority of the arteries appeared to be of approximately the same age.

It is interesting to confirm the changes previously found by others in a vein performing some arterial functions. Reid,[15] in a microscopic study of the regional vessels following experimentally produced arteriovenous fistula, found hypertrophy of the walls of the proximal veins and an increase in the elastic tissue as a result of the assumption of arterial function by the vein. In the present study definite changes were found in the veins, giving them the general histologic appearance of arteries. This would indicate an increase in the venous pressure in these vessels but this was not observed clinically with the crude method used for its determination. It is a question whether changes in the histologic appearance of a vein would occur in the presence of an abnormally high content of oxygen of the venous blood alone, or if such changes depend entirely on the increase in pressure and volume of the blood in the regional veins as a result of an arteriovenous fistula.

The physiologic changes present were of interest chiefly because of the local effects produced and in all probability were due largely to the arteriovenous fistula. General circulatory effects were absent excepting that bradycardia was produced by compression of the fistula. Although the collateral circulation of the upper part of the arm was poorly developed and required further development before operation, the collateral circulation surrounding the arteriovenous fistula was well developed, as indicated by the observation by mercury injections. This accords with Reid's[17] clinical and experimental data that arteriovenous fistula is the most powerful stimulus there is to the development of collateral circulation of the surrounding vessels. The oxygen content of the blood of the regional veins was almost that of pure arterial blood and, as Pemberton and Brown have indicated, is absolute proof of the existence of an abnormal arteriovenous communication.

Calorimetric and surface temperature studies revealed the expected increase in production of heat by the right hand. The excess of arterial blood passing through it was sufficient almost to double the calorimetric output of this extremity over the left. There was a slight increase in surface temperature of the right hand in the area at the base of the index finger. Elsewhere it was considerably colder than the left.

A better understanding of the clinical problems presented by this case is obtained from the pathologic study made. It was obvious that the brachial aneurysm should be attacked surgically but the presence of the arteriovenous fistula increased the hazard greatly for such an attack. It was more than a problem of simply developing the collateral circulation of the arm as a whole to the point of caring for the tissues following obliteration of the brachial artery. It did not seem justifiable, in view of experience in other cases, to attack the arteriovenous fistula directly. Following operation the patient had a great deal of pain in the right hand, the cause of which

was not quite certain at the time. Attempts were made to increase the circulation to the hand by the use of heat locally and typhoid vaccine intravenously, but without success. Thrombosis of the arteries (superficial palmar, radial and ulnar) had occurred and the small amount of arterial blood entering through the collateral channels was being shunted through the fistula before it could get to the fingers. This was well demonstrated by the injection of mercury into the arterial tree following amputation. Before the mercury, under low pressure, had entered any of the vessels of the fingers it had passed into the venous tree. Horton in his studies has found that the normal arterial tree will hold mercury up to a pressure of 75 to 90 mm. of mercury, and in some cases as high as 120 to 150 mm. The injection of the vascular tree in the case presented was carried out at a pressure of less than 10 mm. The venous tree in the normal state, therefore, rarely contains mercury as it does not readily pass through the capillaries at low pressures. These data are added proof of the existence of the arteriovenous fistula, and are of interest clinically in showing that flow through an arteriovenous fistula is accomplished at a much lower pressure than is required for normal flow through a capillary bed.

The pain was undoubtedly due in large part to the thrombosis of the vessels and possibly also to the anemia of the tissues, if the latter will produce pain. It did not seem justifiable to approach the arteriovenous fistula surgically, and as the fistula could not be found anatomically following amputation this judgment proved sound. The only course remaining was amputation, which was carried out without incident.

It does not seem possible, in the light of the anatomic changes, that a better result could have been obtained. The presence of the smaller aneurysms of the radial, superficial palmar and digital arteries was probably without significance clinically although of great interest pathologically.

Summary. The association of multiple aneurysms of the right brachial, radial superficial palmar, common volar digital and volar digital arteries with an embolus in the radial artery and an arteriovenous fistula of the hand is recorded. This combination of changes is of unusual interest to the physician because of its rarity and the many fields that open for investigation, and to the surgeon because of the many difficult therapeutic problems it presents.

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LEUKOPENIA RESEMBLING AGRANULOCYTOSIS WITH RECOVERY.

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Since the description of agranulocytic angina in 1922 by Schultz several clinical reports have appeared illustrating the association of the agranulocytic type of blood picture with various other conditions. Among the most recent is the case of almost complete agranulocytosis associated with sepsis presented by Blumer.[1] Another is the group collected by Farley[2] of 7 cases of depressed bone-marrow function following arsphenamin therapy. A fatal outcome has been the almost universal rule in the typical agranulocytic angina cases, as well as in most of the described variations.

During the past year there have been a number of cases in the wards of the Presbyterian Hospital that approached the agranulocytic type of blood picture, associated with throat infection, but in which recovery took place.

These cases have been so similar in their symptoms, physical signs, and blood picture that they are briefly presented as another variant

in the group of infections associated with depression of the polymorphonuclear leukocytic elements of the blood.

The clinical picture consists of:

1. Several days of fever, slowly rising and swinging, often reaching 103° to 104° F. This fever is associated with no symptoms other than mild chilly sensations, and there are no abnormal physical findings.

2. After several days of the fever, there appear moderately enlarged, soft, tender lymph nodes and spleen.

3. Coincident with the enlargement of the lymph nodes and spleen there is a change in the white blood count with a moderate to an extreme leukopenia and reduction in the polymorphonuclear leukocytes, often reaching an almost complete agranulocytosis. There is a relative increase in the mononuclear cells and abnormal forms are sometimes seen.

4. After the appearance of the lymph nodes and well toward the end of the disease, the pharynx becomes red and sore and on the posterior pharyngeal wall may be seen scattered, round, superficial, whitish spots looking, on the red background, very like Staphylococcus albus colonies on a blood-agar plate.

The disease lasts from one to three weeks and, with but one possible exception, all of the cases have recovered promptly and completely, almost by crisis. The syndrome is somewhat similar to, but not identical with, the disease known as infectious mononucleosis or glandular fever.

Case Reports. Case I.—P. V. (Unit No. 85617), an Italian contractor, aged sixty-nine years, came into the wards complaining of pain in the stomach and loss of weight of six months duration. This was subsequently found, at operation, to be caused by a large inoperable carcinoma.

His blood count on admission was normal: 5,000,000 red cells, 10,000 white blood cells, 83 per cent polymorphonuclears, 17 per cent lymphocytes. For three weeks he was without new symptoms and his temperature was persistently normal. Quite unexpectedly, at the beginning of the fourth week in the hospital, his temperature jumped to 102.4°. The only symptom was mild, scattered pains in the joints. Blood cultures on this day and on the two succeeding days were sterile. The course of his temperature and his blood count is shown in the chart on page 234. On the third day of this acute illness, there was moderate, diffuse reddening of the throat, insufficient to cause symptoms. On the following day, cervical and axillary lymph nodes were noted as being definitely enlarged, soft, and tender. The tip of the spleen appeared below the costal margin. With the high temperature, relatively low pulse rate, lack of symptoms, palpable spleen, and leukopenia, a tentative diagnosis of typhoid fever was made. On the fifth day of this acute illness his throat became sore, and round, superficial, white spots appeared in the pharynx, resembling Staphylococcus albus colonies on a blood plate. At the end of the week the temperature had returned to normal, the symptoms had entirely disappeared, the spleen and lymph nodes had reduced in size, and the acute illness was over. Subsequent blood counts were perfectly normal except for a slight progressive secondary anemia presumably associated with the carcinoma.

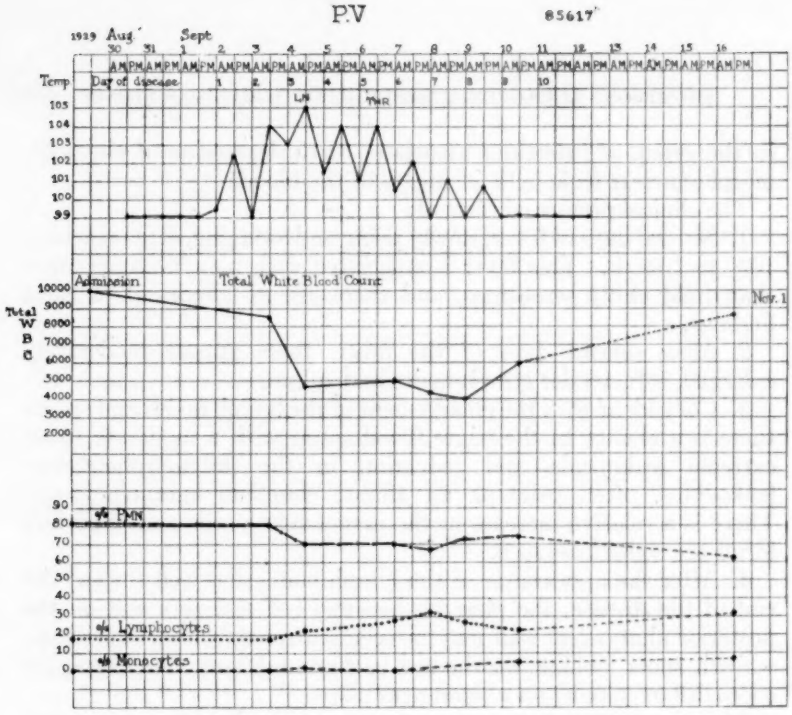

CHART I.—LN, appearance of enlarged lymph nodes. THR, appearance of pharyngitis.

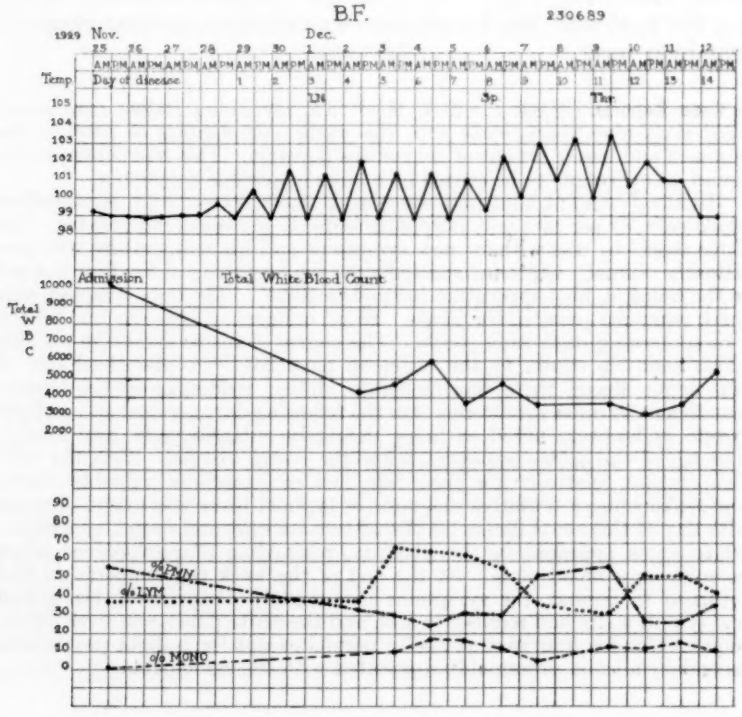

CHART II.—LN, appearance of enlarged lymph nodes. Sp, appearance of spleen; Thr. appearance of pharyngitis.

CASE II.—B. F. (Unit No. 230689), a Jewish subway guard, aged forty years, was admitted to the medical wards as a possible mild exophthalmic goiter. His admission blood count showed 4,700,000 blood cells, 10,300 white blood cells, 56 per cent polymorphonuclears, 37 per cent lymphocytes; no abnormal cells were seen. For the first three days his temperature remained normal. On the fourth day it began to be progressively elevated. The temperature course throughout this acute illness, together with the white blood count, is shown on the chart on page 234. There were no symptoms with the initial rise in temperature and no physical signs to explain it other than a very slightly reddened throat which had been noted several times in the medical dispensary during the two months he was followed there before admission. A blood culture showed no growth. After a week of this unexplained fever, moderate enlargement of the posterior cervical lymph nodes was noted. On the tenth day of this acute illness, the patient was still without symptoms and there was no change in the appearance of the throat. The glands were thought to be even larger and were described as soft and slightly tender. The tip of the spleen could just be felt on deep inspiration. It was not until the twelfth day that his throat was noticed as being more diffusely reddened than previously, and on the day following, small, white, round, superficial ulcerations, resembling Staphylococcus albus colonies on a blood plate, were seen. With the appearance of these, the temperature began falling, reaching normal on the sixteenth day. This was followed by rapid clearing of the throat lesions, prompt regression of the lymph nodes, and a rapid return of the blood count to normal.

These two cases show the complete course of the disease, with an afebrile period before and after.

CASE III.—G. R. S. (Unit No. 85565), a graduate nurse, aged thirty-six years, came into the medical wards with a two and a half week history of chills, fever and scattered, variable aches and pains.

On admission her temperature was 104.6° and she seemed acutely ill. Physical examination revealed slight cyanosis, flushed face, and enlarged, nontender cervical and axillary lymph nodes. The spleen was just palpable, soft, and not tender. The remainder of the examination was negative. The throat was not sore or inflamed. Her admission blood count showed normal red count and hemoglobin. White blood cells numbered 2500, 56 per cent polymorphonuclears, and 44 per cent lymphocytes, with no abnormal cells. On the day after admission, her throat for the first time became sore with the appearance of diffuse redness and scattered, round, white, superficial ulcerations, resembling Staphylococcus albus colonies on a blood plate. The day after admission her highest temperature was 103.6°. The lymph nodes and spleen appeared slightly larger. The leukopenia persisted and 6 per cent of abnormal white cells had made their appearance. Two blood cultures were sterile. It was felt by those who saw her at this time that she was probably developing an acute leukemia. On the third day after admission, her temperature spiked again to 103.2°. At this time there were 4600 white blood cells, 56 per cent polymorphonuclears, 22 per cent myelocytes, and 5 per cent myeloblasts. Her temperature fell practically by crisis on the fourth day, three weeks after the onset of symptoms, and remained normal. Her symptoms rapidly disappeared with a return of the blood count to normal and a regression in the size of the lymph nodes and spleen. She was discharged on the eighth day after admission for further convalescence.

She died suddenly four days after discharge with symptoms suggesting occlusion of a cerebral artery. Autopsy was not obtained.

CASE IV.—S. W. (Unit No. 224143), a student nurse, aged eighteen years, was admitted with a five-day history of headache and general malaise. During these five days, physical examination was entirely negative, the highest temperature being 101.8°. On the fifth day of her illness, previously palpable cervical lymph nodes were thought to have enlarged and become tender. During the five days before admission, she had not complained of sore throat and examination was negative.

Examination at the time of admission revealed a moderately ill young woman with a temperature of 102.6°. The throat was negative. There was moderate enlargement of the cervical lymph nodes, which were soft and tender. The tip of the spleen was just palpable. Her blood count on admission showed 4000 white blood cells, 30 per cent polymorphonuclears, 61 per cent small lymphocytes, and 9 per cent monocytes. The red count was normal and no unusual white cells were seen. No blood culture was taken. Her temperature ranged between 100° and 102°, tending downward. On the tenth day of her disease, there appeared a diffuse reddening of her throat, with scattered, round, whitish spots, resembling Staphylococcus albus colonies on a blood plate. The white blood cells on this day numbered 7000, 24 per cent polymorphonuclears, 66 per cent lymphocytes, and 7 per cent monocytes. The lymphocytes were rather large and suggested slightly immature forms. Her temperature reached normal on the fourteenth day of her disease and she was discharged on the sixteenth day for further convalescence. Her blood count at the time of discharge was as follows: white blood cells 12,500, polymorphonuclears 32 per cent, and lymphocytes 66 per cent.

She returned to work after two weeks convalescence without symptoms or abnormal physical signs and with a normal blood count and differential.

CASE V.—G. M. (Unit No. 74475), an American salesman, aged twenty-three years, entered the hospital with a three-day complaint of scattered aches and pains, mild chilly sensations, and fever. The admission diagnosis was "grippe."

Examination revealed a well-developed and well-nourished young man looking acutely ill. His throat was slightly injected and the cervical lymph nodes were moderately enlarged. The temperature curve and the white blood count are shown in the chart on page 237. During the second week of his stay in the hospital, there was considerable further increase in the size of the cervical lymph nodes, together with moderate enlargement of the axillary and inguinal nodes and spleen. At this time several whitish spots were observed on the posterior pharyngeal wall suggesting Staphylococcus albus colonies on a blood plate. These disappeared promptly after the return of temperature to normal. Two blood cultures taken during the febrile stage were negative.

He was seen in the medical follow-up four months after discharge from the wards, at which time he was without symptoms or physical signs of any kind.

Case V is the only one of the group that did not have a severe leukopenia during the entire illness. This case more than any of the others suggests the syndrome known as glandular fever. This diagnosis was seriously considered during the patient's stay in the wards, but it was felt by most of those who saw him that the clinical picture was not quite typical of that disease as it has been described in the literature and as it has been seen in this hospital.

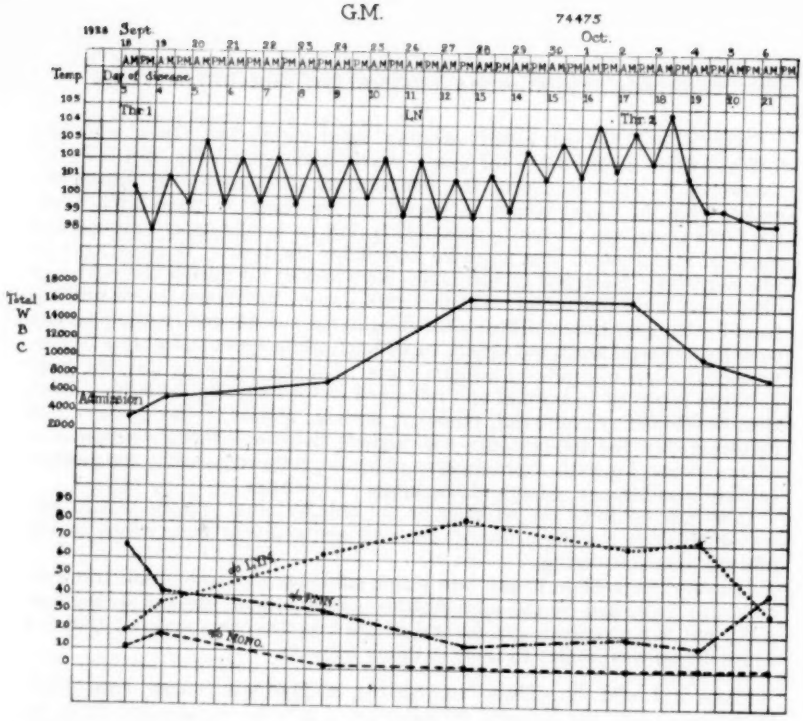

CHART III.—LN, appearance of enlarged lymph nodes. Thr. appearance of pharyngitis.

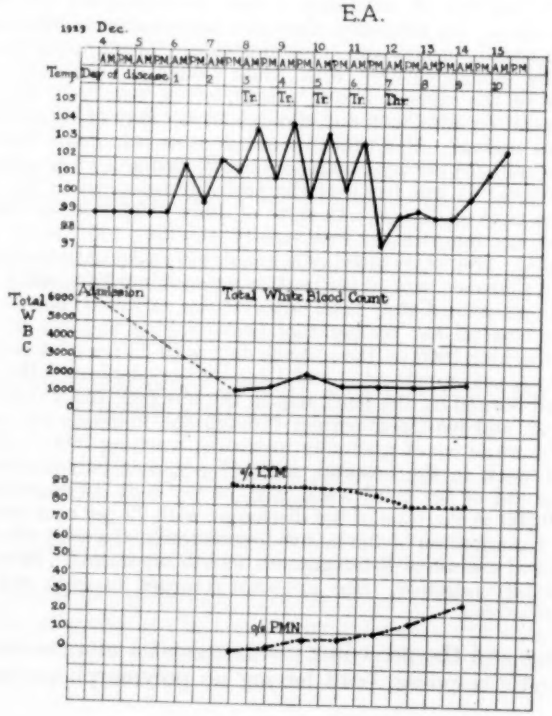

CHART IV.—Tr. transfusion of blood. Thr. appearance of pharyngitis.

CASE VI.—E. A., an elderly woman, aged eighty-two years, who had had a cardiac insufficiency for many years suddenly developed a fever on December 6. The course of the temperature throughout the illness, together with the blood count, is shown on the chart on page 237. With the fever there was moderate prostration, but no localizing symptoms, and physical examination was negative except for the heart. A blood culture was negative. Enlarged lymph nodes were looked for during the course of illness and were not found. On the sixth day of the illness, there was noticed for the first time a diffuse reddening of the throat, and on the pharynx were seen several scattered, small, superficial, white spots resembling Staphylococcus albus colonies on a blood plate. On the following day the temperature returned to normal and remained so for forty-eight hours. There then developed symmetrical, pustular, necrotic lesions in the groins. The following day the temperature was higher, there was rapidly progressive edema of one leg with a progressive phlebitis, followed shortly by marked cardiac insufficiency, edema of the lungs and exitus.

It is impossible to say whether or not this terminal episode was in any way related to the immediately previous acute illness from which it was felt she was recovering.

It is also impossible to say how much influence the daily small transfusions may have had on the temperature. This patient was not in the hospital, but her physician saw several of the hospital cases and felt that her acute illness was similar to them in many respects.

CASE VII.—M. K. (Unit No. 85876), a graduate nurse, aged forty years, came into the hospital complaining of general malaise and fever for one week. Since the time of onset of symptoms there was a small white spot on her gum which slowly spread, in spite of treatment with silver nitrate. On the day of admission a new spot appeared and salivation became excessive. On admission she had a temperature of 99.6°, pulse 96, and she appeared flushed and uncomfortable. There were two shallow ulcers in the mouth covered with white slough. There was moderate enlargement of the cervical lymph glands, which were very tender. Her red blood count on admission and throughout her stay of four weeks in the hospital was normal. Her white blood count on admission showed 2800 white blood cells, 73 per cent lymphocytes, 27 per cent monocytes, 0 polymorphonuclears. It was felt that she probably belonged to the agranulocytic angina type of disease. In spite of daily phlebotomies, followed by transfusions, her temperature rose rapidly, reaching 105° on her fifth day in the hospital. Her white blood cells had slowly fallen until they numbered but 1200 on that day, with 2 per cent polymorphonuclears and a very rare myelocyte. An immediately fatal outcome was expected, but on her sixth day in the hospital her temperature began falling and her white count increased, reaching 2900 on the seventh day, with 25 per cent polymorphonuclears, 8 per cent myelocytes, and 1 per cent myeloblasts. Her temperature reached normal on the tenth day in the hospital, the seventeenth day of her illness, and remained normal through the following two and a half weeks. The white count gradually increased, reaching 7000 by the end of her second week in the hospital, with 58 per cent polymorphonuclears; 9000 at the end of her third week, with 66 per cent polymorphonuclears; and was 10,300 at the time of her discharge, with 72 per cent polymorphonuclears. Examination of the mouth lesions revealed a very few Vincent's organisms and a mass of heterogeneous mouth organisms. Blood cultures were repeatedly negative. She has since returned to work and has been without symptoms.

This case and the preceding one represent a more severe type of agranulocytic response, both having no polymorphonuclear leuko-

cytes over a period of several days. These 2 cases probably more closely belong to the accepted syndrome known as agranulocytic angina than do the others.

Bacteriology. Attempts to obtain bacteriologic information have been unsuccessful. The throat lesions have been cultured in every instance and a variety of organisms obtained. A few hemolytic streptococcus colonies were isolated in 2 of the patients, but were not found in the other 4. The whitish, round, very superficial ulcerations observed on the posterior pharyngeal wall were removed as carefully as possible in 3 of the cases and examined by culture and direct smear. The cultures revealed a mass of common mouth and throat organisms without any particular predominate one being found. Direct smears revealed necrotic tissue with scattered various bacteria. These ulcerations were examined for Vincent's organisms in all cases and these were demonstrated in small numbers in three instances. As these organisms are frequently found in any ulcerative condition of the mouth or throat, it was not felt possible to attribute any particular significance to their presence.

Discussion. The syndrome as observed probably represents an unusual reaction on the part of the hematopoietic system to transient throat infection. It is not uncommon to see general systemic reaction preceding, by several days, signs of local inflammation in infections of this sort and this syndrome seems best explained on that basis.

Conclusion. Seven cases are presented of an acute, transient, infectious disease associated with high fever, low pulse rate, enlargement of the lymph nodes, leukopenia, and relative agranulocytosis, the late appearance of queer whitish spots on the posterior pharyngeal wall, and prompt, complete recovery. The etiology is unknown. They represent another variant in the group of infections associated with the agranulocytic type of blood picture.

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PSYCHOGENIC FACTORS IN THE ETIOLOGY OF ULCERATIVE COLITIS AND BLOODY DIARRHEA.

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In the course of psychologic investigations in relation to disease—part of the program of the Constitution Clinic—our attention was drawn to a number of cases of ulcerative colitis admitted to the

hospital wards. Preliminary studies directed toward the personality makeup in these patients gave many indications that there were deeper problems to be investigated in the psychophysiologic sphere. Accordingly, thereafter, more emphasis was placed on the patients' life histories and the development of their symptoms. The first four histories obtained are briefly given below, together with an abstract of the physical findings and hospital record. What appears in these cases is a well-marked time relationship between the outbreak of an emotional disturbance and the onset of the symptoms.

For example, in the first case, E. P., an only child, notices the first shreds of mucus in her stools on the very day on which she becomes secretly married. In the second case, C. M., unconsciously conditioned against marriage, finds blood in her stools soon after becoming interested in her first suitor. Later, when engaged to a second one, she develops severe diarrhea with cramps and bloody stools which force her to go to a doctor a few days before the date originally set for her wedding. The case of J. H., is practically the same. In the last case, a boy, aged eighteen years, with a past history showing association of diarrhea with fear, notices blood in his stools from two to five days after a fellow worker threatened to murder him.

The objective side of these histories is all that can be given in a short paper. But the practitioner who has taken the trouble to gain insight into the mechanisms and mannerisms of neurosis will appreciate the subjective feelings which precipitated the pathologic responses in each case.

Case Reports. CASE I.—E. P. ABSTRACT OF MEDICAL RECORD. A married woman, aged twenty-five years, first admission, complaining of diarrhea and vomiting of five days' duration. She had "cholera infantum" in infancy, and three years ago, while abroad, she experienced a bloody diarrhea of two weeks' duration. At other periods of her life she has been constipated, very much so, in fact, since her year abroad, with perhaps only a dozen spontaneous movements in three years. In other respects her health has been excellent. She was married a few months ago, and her last period, due nearly a month ago, was almost completely missed. She has noted no breast changes and does not think she is pregnant, though Dr. X. thinks she may be six weeks along. She was well until a month ago, when she began to note increasing constipation associated with severe, intermittent, abdominal cramps. She went to a hospital, where they gave her a course of colonic therapy; these treatments began to provoke nausea and vomiting, which has grown progressively worse. Four days ago she suddenly began to have diarrhea. Her physician reports: "Stool very foul. Composed of pus, blood and mucus. No amœbæ on one examination. She vomited everything taken by mouth, and the cramps became much more severe. She has not slept much, in spite of morphia. No medications, not even water, have been retained."

Physical examination revealed a well-developed and well-nourished young woman looking quite ill. She was writhing with intermittent abdominal cramps and retching at intervals. There was evidence of moderate dehy-

dration. The abdomen was flat, soft and generally very sensitive to light pressure. No other positive physical findings were noted. Temperature, pulse, and respirations were normal. Her urine contained large amounts of acetone bodies. Blood count normal. Her vomitus gave a faintly positive guaiac reaction. Stools were brown, semifluid, guaiac-negative. No amœbæ seen.

The admission diagnosis was, "acute colitis" (amebic?), acidosis, pregnancy (?)

The diarrhea cleared up almost immediately after admission, but severe cramps and vomiting continued. She was treated with glucose and saline intravenously and subcutaneously and guarded administration of fluids by mouth. Stools were repeatedly negative for amœbæ. The diagnosis of pregnancy was established by gynecologic consultation. A psychologic consultation was requested because the patient managed to give an impression of something obscurely amiss in her marital history and response to treatment.

After a week on the medical wards she was transferred, somewhat improved, to Sloane Hospital for Women.

Total stay in Presbyterian and Sloane Hospitals twelve days.

Life Situation. The patient is the only child of strict, adoring parents in Georgia. In her final year at college she had a boy friend, but her friendship with him had been marred by the following incident: The young pair had once been stranded at night—too late for her to return to her dormitory. So they had gone to a hotel together to spend the night. Although they had had no sex relations she felt very guilty and apprehensive over the whole affair and wanted to sever all connections with her admirer, but he threatened her, saying: "I will never let another man have you—I will expose you, and no one will believe that we did not have relations that night." From this incident she dates the onset of constipation and her present practice of giving herself a daily enema.

On graduating, she took a position as teacher in an American school in the Near East. She answered the daily letters of her boy friend once a month, still feeling herself in his power, in spite of her effort to get away. Meanwhile the young man had been dismissed from college, had lost one or two jobs, and finally, pining for her love, he had lost his health.

After a year's teaching abroad, she was called home because of her father's illness. She taught school near home for another year, and consented during this period to see her suitor at long intervals. The situation was a great strain upon her, and at the end of the year she came to New York, eager for a stage career, but she needed money first and took a position as cashier in a chain-store.

A cowboy from the West, driver of an armored car, came every evening to collect the money from her cash register, and fell in love at first sight and wrote her, asking for an appointment two weeks ahead. She received him in her rooms. From the first moment he made vain attempts to seduce her but at last he said: "You have stood the crucial test—you must marry me." A month later they were married secretly. On that eventful day she first noticed long shreds of mucus in her stools. Two months after, she heard that her father had died and went South, but she still withheld the news of her marriage from her mother. By the time the young woman got back to New York she found she was pregnant and noticed blood and pus in her stools. Within three days after admission to the hospital she had decided to inform her mother of all that had happened and her colitis had disappeared.

Case II.—C. M. Abstract of Medical Record. An American secretary, aged thirty years, admitted because of abdominal cramps and diarrhea

of two months' duration. Patient has lived on Long Island most of her life, never in tropics. Always had a hypersensitive nervous system, subject to aches and pains. Four years ago blood streaked stools noticed: blood present intermittently until eight months ago when clots were passed. During this time she was treated for constipation. For two months she has had severe abdominal cramps, urge to defecation with passage only of mucus in many instances, bowels move about 18 times a day. Sent in by her local physician who is said to have found Amœba histolytica in rectal mucus. Lost about 22 pounds in eight months.

Physical Examination. Temperature, 99.4; pulse, 80; respirations, 20; blood pressure, 105 systolic, 70 diastolic. Looks chronically ill; tongue is coated; examination otherwise not remarkable, except for slight diffuse tenderness over the entire right abdomen, no spasm.

Laboratory Findings. Hemoglobin, 68 per cent; red blood cells, 4,390,000; white blood cells, 11,000; polymorphonuclears, 55 per cent; leukocytes, 31 per cent; mononuclears, 6 per cent; eosinophils, 8 per cent; urine negative; Wassermann negative. Stool: red blood cells, ++++; white blood cells, ++++. Several questionable nonmotile Amœbæ histolytica (?) seen. Proctoscopic examination revealed multiple ulcers of rectal mucosa, typical of amebic colitis, no amœbæ found at proctoscopic examination. Gastric expression: Free hydrochloric acid, 0; total, 16.

Course. After a week's observation put on yatren by mouth and by rectum, receiving 41 gm. in two weeks. Though cramps were relieved somewhat, stools continued about five a day, and continued the same after yatren had been discontinued for a week. She then received stovarsol, 7 gm., in the course of a week, following which her diarrhea and cramps disappeared. However, she developed an arsenic dermatitis, which had practically cleared up at the time of discharge two weeks later, following sodium thiosulphate. A second proctoscopy before stovarsol was started showed some healing, no amœbæ found. During stay here her emotional makeup was found to be unstable, and she was irritable frequently. Due to rapid improvement under stovarsol, it was considered probable that her colitis was amebic in spite of no definite amœbæ having been found here.

Diagnosis on discharge was, chronic colitis; acute poisoning by stovarsol.

After discharge from the hospital the patient was married and three weeks later diarrhea returned with blood and she soon had thirty stools a day. She was treated in another city with emetine and stovarsol and gradually improved, having during the exacerbation of her illness lost over 30 pounds. This recurrence of her illness lasted for about four months. For three months she has been perfectly well and has a job here in town. She appears to have a better slant on life and is more composed though even now she avoids intercourse because of a fear that she may have a deformed child. She is careful to avoid raw fruits and coarse foods but except for this she has forgotten her gastrointestinal tract.

Life Situation. The first conferences with this patient revealed very little except that when she was four years of age her mother died of pneumonia. She was pleasant on all other subjects but touchy about her personal history. "I have supported myself since I was seventeen," she would reply, "and my family affairs have nothing to do with the case." Finally, however, she abandoned her resistance and gave the following history:

Three years ago her men friends in the office tried to plan a match for her with another officer in the company. Without having much affection for this person she did, however, go out with him several times, and the thought of marriage as a possibility occurred to her for the first time. Soon after, the duration of her menses diminished to two days and she noticed blood in her stools. She was afraid that the blood was a symptom of cancer, nor would she accept the reassurance of several doctors—none of whom, she thought, took her fear sufficiently seriously.

Two years later she met another man to whom she promptly became engaged during the Christmas season. They planned to get married "in about a year," although there was no tangible reason for such a long engagement. During that year her menses diminished to one day. The year wore on and a few weeks before the following Christmas, she returned from an extended trip. Her sweetheart met her. He had looked up several apartments which he wished to show her, but she could take no interest in choosing between them. She was whole-heartedly in love, but no definite day had been set for the wedding and she was tending to put off the event more and more. Meanwhile, after her return, her colitis became suddenly worse, and a few days before Christmas she went to a doctor for the first time during that year. She was having eight stools a day and was beginning to have cramps, and was admitted to the hospital.

The psychologic background of her case is interesting, not in its novelty, but as a classic. From what has been said, the possibility suggests itself that her fear of cancer derives its exaggerated mental energy from a fear of having a child. When questioned about this she said that the thought of childbirth was, in fact, a mortal fear—she was sure she would die if she had a child. At first she could not account for this. She said she knew practically nothing about sex or childbirth until three years ago. She was asked to think about this problem—how death and childbirth had become so indelibly associated in her mind, but it was not until the following day that she remembered that her mother's death from pneumonia (?) had occurred two weeks after the birth of the patient's youngest sister. She had never thought of that before!

Her aversion to marriage, partly unconscious, also involved a fear of sexual relations, and this fear was likewise definitely conditioned. The patient was the fourth child in a family of six. After the mother's death the father engaged a neighbor to come in as housekeeper, and when the patient was about five years of age, the father married the housekeeper. She was a jealous woman—the children would not kiss her and so she forbade them to kiss the father, whom they adored. When it was pointed out to her that this wound to her early love had come about exclusively through the sex factor—that is, the marriage of the father—she declared: "But that wasn't the worst blow" and then recounted the following story:

When she was about seventeen years of age, her older brother, by that time the only one of the older children still living at home, went away for four years in the navy. She had not been unduly attached to this brother, but during his absence the two had a very voluminous correspondence. In due time the brother returned full of plans to buy an automobile, build a garage, and so on. He was welcomed by his sister as a savior. She and her two younger sisters had borne the brunt of the stepmother's nagging for four years. The first day after his arrival they measured out the site for the garage. But the dreams were not to come true, for within a month the brother was engaged to the stepmother's cousin—a woman ten years older than himself—who "had made a dead set for him, vamped and mothered him."

The patient never spoke to him again. For a while she would lock herself into her room when the brother was home, and he would plead with her through the door. On one occasion he told her that in his four year's service he had not had intercourse. This remark increased her fury—it was the first time she had ever heard the word, but she said she sensed its meaning right away. Soon after this she left home for good. This episode is clearly a repetition in its essential details of the earlier psychic trauma. Again sex had robbed her of what she cared for most.

Case III.—J. H. Abstract of Medical Record. This is the first admission of a thirty-three-year-old American butcher. Four years ago

he began to have diarrhea and a burning sensation in his rectum. Following this, blood and mucus were passed. He had much tenesmus and passed 3 to 8 stools a day. The condition has persisted almost unchanged since its incipiency, except for a few months last summer following certain rectal treatments. He has lost about 40 pounds but most of this has been regained.

P. X.: A well-developed and well-nourished man not appearing ill. Teeth good, tonsils buried. Lungs and heart normal. Abdomen normal. Prostate large and firm. Rectal mucosa: hyperemic, few bleeding areas and shallow ulcerations, some scars.

Laboratory Findings. Red blood cells, 3,740,000; hemoglobin, 88 per cent; white blood cells, 8200; polymorphonuclears, 52 per cent; eosinophils, 7 per cent; Wassermann, negative. Stools: few Entamœba histolytica found, guaiac negative on admission, then ++, then negative. No dysentery bacilli or enterococci. Chest Roentgen ray negative. Urine negative.

Course. He was a proven case of amebic colitis and was therefore given an adequate course of yatren. The drug seems to have been highly successful in this case. On discharge the rectal mucosa was perfectly normal and no amœbæ found. Patient feels in fine shape.

Diagnosis on discharge was, chronic colitis.

The patient, since his treatment with yatren, has had no return of his symptoms for one year, with the exception of some burning in his rectum with attending looseness of stools and constipation for a week following the death of his mother. He has worked continuously since discharge from the hospital.

Life Situation. The patient is of a very mild, quiet temperament—a salesman in a grocer shop. When he was twenty years of age his father died, and since then he has lived at home with his mother and sister. In fact, he has only been away from his mother for two weeks in his life. When asked if he had ever thought of marriage, he first said he could never leave his mother and sister. But later he said his colitis prevented his getting married. It turned out that four years ago he began keeping company with a girl who lived around the corner. Within a month or two his diarrhea set in, and he stopped work for eight weeks. For two years he averaged about six stools a day—he said his condition was always worse when he resumed the responsibilities in the event of the boss's absence.

Then followed a period free from symptoms. Six months of good health brought him the courage to propose marriage to the girl who had been setting her faith in him for about three years. Her birthday was six weeks off, so he promised to give her a ring on that day. He promptly got the ring, but alas, he got a return of his colitis too. This time he came to the hospital where it was discovered that he had amœbæ in his stools, and where he was cured by specific treatment.

This case shows that the course of the chronic infection is influenced by psychologic factors. Moreover, it is not impossible that the patient's emotional conflict, affecting the gut through disturbed vasomotor, secretory, or peristaltic function, may have lowered the original resistance to the invading organisms.

Case IV.—I. S. Abstract of Medical Record. A Russian-born Jewish boy, aged eighteen years, first admitted to the hospital June 21, 1928, complaining of bloody diarrhea of five weeks' duration. His past history included typhus, malaria, and scarlet fever in childhood. He came to this country six years ago. His general health had been good up to the time of present illness, but he was of a nervous disposition and, following periods of fear or worry, had noted attacks of abdominal cramps and tenesmus. His occupation was that of a newspaper photographer, strenuous and often exciting work, with irregular hours.

Seven weeks before admission he began to have marked belching after meals; two weeks later he noticed dark-red blood in his stools; stools became loose and more frequent. Dietary treatment by his local physician was ineffective. Two weeks before admission he was having 12 to 13 watery stools a day accompanied by severe abdominal cramps. Stools contained blood and mucus. Weakness and occasional vomiting during preceding three days.

Physical examination showed a thin pale Jewish boy, mildly acutely ill, but in no apparent discomfort. Tongue clean, heart rate somewhat rapid, abdomen soft, not distended, with moderate generalized tenderness on deep pressure. Pulse, 96; temperature, 99.6°; blood pressure, 110 systolic, 50 diastolic; weight, 115 pounds. Blood count: hemoglobin, 55 per cent; red blood cells, 3,150,000; white blood cell, 7500; polymorphonuclears, 64 per cent; lymphocytes, 27 per cent; eosinophils, 9 per cent. Slight pallor of red cells. Blood Wassermann, negative. Blood Widal, negative. Stool: fluid, dark red bloody material. Microscopic examination: loaded with red blood cells and pus cells. Guaiac ++++. Stools negative for amœbæ, Bacillus dysenteriæ and Bacillus typhosus.

Course. Patient ran an irregular fever, up to 103°, and continued to have frequent bloody stools, abdominal cramps and anorexia. Apprehensive and depressed. Several transfusions seemed to help his condition somewhat. Mental attitude and general condition improved after psychotherapy was started. Discharged improved, though he still had some bloody diarrhea, on July 21, 1928.

Readmitted nine days later with the symptoms of pain in left flank, blood-streaked stools and nausea. Examination showed increased tenderness over whole colon. Weight, 110 pounds; hemoglobin, 38 per cent; red blood cells, 2,050,000; proctoscopy showed several large superficial ulcers covered with mucopurulent exudate.

Course. Temperature normal, except for a reaction following transfusion. Spleen became palpable. Given belladonna and a course of yatren, also Blaud pills. He improved and gained in weight. Stools 4 to 6 daily, but without blood. Discharged and went to the country August 28, 1928.

Through the autumn patient did fairly well, gained weight up to 140 pounds, continued to have frequent stools with blood and pus.

Third admission December 31, 1928, for special study, culture of stools, etc. Proctoscopy showed edema of mucosa, and multiple miliary abscesses. Cultures of stools were taken. Discharged January 11, readmitted January 21, 1929, and vaccine and filtrate injections (prepared according to Bargen's technique) were given. General course unchanged. Discharged February 5, 1929.

Vaccine injections were continued three times a week. Patient's abdominal condition was about the same but his anemia increased. Readmitted March 8. Following transfusion, blood count improved to hemoglobin, 56 per cent; red blood cells, 4,300,000. Again his diarrhea improved, but anemia and weakness increased during the next two months. Hemoglobin, 28 per cent; red blood cells, 2,800,000.

Readmitted for the sixth time June 7, 1929. Pale and chronically ill. Abdomen soft, with marked tenderness in left lower quadrant. Temperature, 103°; pulse, 120.

Course. Tenderness over whole colon became acute and remained so. Stools contained only traces of blood. Patient continued to run an irregular fever, developed a profound toxemia and prostration, was unable to take nourishment and wasted rapidly. He developed a marked glossitis, and a curious and unexplained subcutaneous edema of the cervical and anterior thoracic regions. Transfusions and other measures were ineffective. As a

last resort, ileostomy was performed on July 15; after this he seemed to improve slightly, but weakened again and died July 21, 1929.

Final Diagnosis: Chronic colitis, secondary anemia.

LIFE SITUATION. In the first interview the patient said he had worked in a machine shop in a basement for two years without a vacation. He went to high school evenings. Sundays he did special work near his home. He is the sole support of his mother and sisters, with whom he emigrated from Russia six years ago. The patient remembers it was on December 15 he noticed blood in his stools for the first time. Five months later he began having severe cramps and diarrhea and entered the hospital.

Referring to his childhood, the patient described the cramps which he had felt at the times, when, in Russia, the Red Army had looted his home. Eventually he and his family were thrown out of the home, and shortly after this he contracted typhus. In the process of talking about these episodes, the patient had what he said was the most severe cramp he had ever experienced. He remembered also having diarrhea in infancy and how, at the time, his nurse used to blacken her face to frighten him into eating the raw eggs which were prescribed. He denied any other frights or fears.

In the second interview, however, he told of how his boss had hired a helper for him in the fall. The helper was a moron or half insane, the fifty-year-old brother of the boss. The patient had to instruct him in the routine of the work, but he made many mistakes for which the patient, who did not dare complain, was blamed by the boss. One day, about December 10, (that is, about five days before the first appearance of blood in the stools) the helper, during a quarrel, threatened to kill him. For two months he had to work alone in the basement with this madman. When he felt especially nervous he would take refuge in the toilet. Finally the boss saw for himself that his brother was no asset to his business and therefore fired him. But the patient's fear was not relieved because the next day the janitor told him that the brother had said he was coming down some day to knife him.

The patient had always quarreled with his boss, who was very cranky, and now things were becoming intolerable. But his family being entirely dependent upon his weekly earnings, he had to put up with it all until his colitis settled the question for him.

Discussion. It is well known that a state of emotion is often accompanied by hypermotility or spasticity of the colon and probably also by hypersecretion and vasomotor disturbances.[1, 2, 3] The exact mechanism of this phenomenon is unknown, but the reality of an actual nervous link between mental states and colon disturbances is virtually proved by the abundance of histories which reveal a close time relationship between the mental and physical symptoms. The cases reported above show this relationship in a very striking manner, but more than that, they show how serious the physical condition can become in one or more of the following circumstances, namely: (1) if the emotional conflict is deep-seated, or chronic or not easily settled; (2) if there is a specific organism, and, vague though it is, we must add, (3) if the individual is predisposed in some way by heredity early training, general physical or nervous makeup, etc., to colon afflictions.

In connection with this third factor there were some noteworthy personality characteristics which were common to 12 patients which I observed. Draper and McGraw[4, 5] have emphasized the

fear component in cases of gastric ulcer and this observation especially would apply to cases of bloody diarrhea and ulcerative colitis. They describe the gastric-ulcer type as one showing "little stability of mood, rapid expenditure of emotional energy, quick adjustment to changes in the environment and great fearfulness. The ulcer patients are ideal opportunists and mental sprinters; and while they have little endurance, they are promptly rehabilitated by food, short periods of rest and the relief of anxiety."

The outstanding trait in colitis patients, besides fearfulness, is their emotional immaturity, and in this respect they differ from the gastric-ulcer individuals who give the impression of a greater emotional development. It goes without saying that diarrhea is an infantile response to fear. The organization of the infant is presumably such that fear is often expressed by excitation of the colon, and thus a pattern may be laid down and not outgrown.

Aside from their physical symptoms, the colitis patients revealed definite childish elements in their makeup. Of 7 men who were interviewed, all were tied to their mothers except one who had found a mother substitute in an older sister. Several of these men had never been away from their mothers for more than thirty days in their whole lives. None of these men were married, and for the most part the onset of their colitis was associated with the conflict between the mother-tie and desire for marriage—psychologically a repetition of the birth experience. Of the 7 men, the presence of ulcers was proved in 5 cases, and the persistent appearance of bloody stools in all. Our language sums up the story of these patients in the phrases "They feel cramped" and "They haven't got the guts."

Of 5 women with bloody stools, in 2 of whom the presence of ulcers was proved in the hospital, 3 were married as follows: One to a man her own age who had been virtually living in the home of his wife's parents; the second was married to a man twice her age—an inadequate father substitute—from whom she tried to free herself, but got colitis in the attempt; the third, E. P., was secretly married. Of the remaining 2 women, one, C. M., was engaged, but her colitis and her unconscious mental attitude were interfering with marriage. The other was unapproachable on the subject of marriage so I could infer very little as to her conscious attitude about this matter, or in fact any other matter.

Although nothing can be absolutely proved as yet from these cases, the evidence is very suggestive that the more severe cases of colitis with bloody diarrhea and ulcerations have a psychologic factor in their etiology of the kind similar to that which has long been recognized as existing in some simple diarrheas and in mucous colitis.

Prolonged psychoanalysis is usually economically out of the question for ward patients who cannot afford the time for it. But

we have nevertheless been encouraged to put greater effort into work along psychotherapeutic lines not only while the patients are undergoing intensive medical treatment in the wards, but also after their discharge from the hospital by interviews in the out-patient clinic.

Conclusions. Investigation into the life histories and mental attitudes of a series of 12 patients suffering from bloody diarrheas or ulcerative colitis revealed a close association in time between the emergence of a difficult psychologic situation and the onset of the symptoms.

Mental conflicts concerned with marriage were more commonly found than other types of situations which might evoke anxiety. In each case the patients faced their problems in an inadequate, infantile manner.

If the pathologic process has not progressed too far, a thorough investigation into the patient's life and mental attitude is indicated and may afford opportunity for much-needed psychotherapy.

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A NEW INTERPRETATION OF THE VAN DEN BERGH REACTION.

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Many attempts have been made to explain the differences in reactivity of sera from jaundiced individuals with a sulfanilic-nitrous acid diazo reagent when this reagent is added directly to the serum. Van den Bergh[1] and McNee[2] believed that two types of pigment were involved, a rapidly reacting type in obstructive jaundice and a slowly reacting type in hemolytic jaundice. On this basis the reaction was advocated as a method for the differential diagnosis of jaundice. Other explanations for the prompt and delayed type of

reactions have been based on differences in solution state of the pigment, the extent of its combination with base, adsorption on serum proteins, and the effect of bile salt accumulation in the serum in obstructive jaundice. It was shown by Thannhauser and Andersen[3] and Davies and Dodds[4] that state of oxidation and by the latter also, that hydrogen ion concentration were important factors in determining the velocity of reaction. However, none of the explanations previously given are adequate and most of them have been discarded.

For the estimation of bilirubinemia in this laboratory the icterus index has been determined in conjunction with van den Bergh's direct procedure. A close relationship, dependent on the concentration of bile pigment, was observed between the two tests. Immediate reactions practically always occurred in sera having high icterus indices, while delayed reaction sera invariably had low indices. Biphasic reactions were associated with intermediate icteric index values. The possible effect of concentration was recognized by van den Bergh[1] who cites experiments in which sera from individuals having obstructive jaundice were diluted to a light yellow color, but continued to give an immediate reaction. Hence he concluded that the differences in reactivity were not dependent upon differences in the amount of bile pigment present. The degree of dilution in his experiments is not stated, but it could not have been great or the reduced buffering capacity of the serum would have checked the reaction. Only a few experiments were made by van den Bergh and no other investigation of this phase of the diazo test for bilirubin has been found. There is abundant evidence from other sources that concentration is of the greatest importance. Mann, Sheard, and Bollman[5] in their studies of blood bilirubin noticed that the serum gave first a delayed and later a biphasic reaction following the removal of the abdominal viscera. During the same interval the bilirubin content of the serum was increasing rapidly. Barron and Bumstead[6] and Mayo and Greene[7] after obstructing the common ducts and excluding or removing the gall bladder obtained first delayed or biphasic and then immediate* reactions as the jaundice increased. The clinical observations of Friedmann and Strauss[8] and Mogena,[9] who found that the van den Bergh reaction changes with the severity of jaundice, give additional support to the concentration hypothesis.

An experimental study of bilirubin solutions by means of the van den Bergh test has confirmed the importance of the concentration of bilirubin and has shown that it is the principal factor which determines whether immediate, biphasic, or delayed reactions will occur.

Methods. Icterus index determinations were done by the technique described by Murphy.[10] Phosphate buffer solution (pH 7.4)

* "Direct" is used in both papers in the same sense as prompt or immediate.

was used in place of 0.9 per cent sodium chlorid for diluting the serum. When the icterus index was greater than 25 the serum was diluted until it matched the standards between 10 and 15. Kerppola and Leikola[11] have pointed out that bilirubin behaves as an indicator, consequently the color intensity of a bilirubin solution does not indicate the true quantity of pigment unless the pH is controlled.

For the direct or qualitative van den Bergh test the procedure of Lepehne, described by McNee and Keefer,[12] was used. A sheet of paper used as a background was helpful in following the development of color in the tubes. The time required for the color to appear and the time at which it reached its maximum intensity was measured with a stopwatch. The tests were done not longer than eight hours after taking the specimen. Temperature of the reacting materials was controlled in the experimental work, but was neglected in all except the more recent determinations included in Table I. The effect of temperature on the rate of reaction will be discussed later.

The reactions were classified as *immediate* when the color appeared promptly and reached a maximum within sixty seconds; *biphasic* when the color appeared promptly but required more than a minute to reach maximum intensity; and *delayed* when the initial color appeared later than one minute but before five minutes. Reactions starting after five minutes were called negative. Extending the observation period beyond this time introduces possibilities for error due to side reactions. It was often difficult to decide whether a given reaction was immediate or biphasic, hence the term *immediate-biphasic* was used in the tables to describe those instances in which the distinction could not be made.

Relationship Between the Qualitative van den Bergh Reaction and the Icterus Index. In Table I the results of 721 parallel determinations of the van den Bergh reaction and the icterus index are classified according to the type of reaction occurring within selected limits. These tests represent clinical determinations of this laboratory made over a period of five years by six workers. They were done for the most part without special precautions to control color development, temperature, or age of the specimen. Although there is some overlapping in the table the relationship between concentration of pigment and the type of van den Bergh is clearly defined. The overlapping is explained by the many possibilities for experimental error and by the well known difficulty of determining the type of some reactions.

Dilution Experiments with Bilirubin Dissolved in Serum. In these experiments the bilirubin* was dissolved in a slight excess of $\frac{N}{10}$ sodium hydroxid, after which the excess alkali was neutralized with

* Three samples of bilirubin were used. Two were obtained from the Eastman Kodak Company and one from the Theodor Schuchardt Chemische Fabrik.

$\frac{N}{20}$ hydrochloric acid. The slight change in color from an orange to a yellow and the simultaneous formation of a precipitate was used as an endpoint. The precipitate was then redissolved by adding 1 drop of $\frac{N}{10}$ sodium hydroxid. The resulting solutions were faintly alkaline to litmus and acid to phenolphthalein. They were made as quickly as possible so as to avoid the auto-oxidation which takes place in alkaline solution. This concentrated solution was added to clear unhemolyzed human serum. Various dilutions were prepared from the resulting mixture by adding portions of it to serum. In this way a graduated series of serum solutions of bilirubin was obtained. These were treated with the diazo solution as described above, except that it was necessary to increase the reactivity by the addition of alkali in order to obtain reactions having rates comparable to those in jaundiced serum.

TABLE I.—THE RELATIONSHIP BETWEEN THE ICTERUS INDEX AND DIRECT VAN DEN BERGH REACTION.

Icterus index.	Total number.	Van den Bergh.							
		Negative.		Delayed.		Biphasic.		Immediate.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
1– 3	20	19	95	1	5				
4– 6	174	149	85	25	15				
7– 9	89	35	39	51	57	3	4		
10– 12	67	4	7	53	79	10	14		
13– 15	26	..	..	15	57	11	43		
16– 18	13	1	8	3	23	9	69		
19– 25	45	1	2	3	7	40	89	1	2
26– 35	41	..	..	6	15	32	78	3	7
36– 45	37	..	..	2	5	25	68	10	27
46– 55	22	..	..	1	5	13	59	8	36
56– 65	27	..	..	..	..	13	48	14	52
66– 75	23	..	..	1	5	4	13	18	82
76– 85	12	..	..	..	..	1	8	11	92
86– 95	25	..	..	..	..	3	12	22	88
96–105	18	..	..	..	..	2	11	16	89
106–115	16	..	..	..	..	2	12	14	88
116–124	15	..	..	..	..	..	..	15	100
125–135	6	..	..	..	..	..	..	6	100
136–145	15	..	..	..	..	1	7	14	93
146–155	6	..	..	..	..	..	..	6	100
156–165	—								
165–175	4	..	..	..	..	..	..	4	100
176–185	5	..	..	..	..	..	..	5	100
186–195	5	..	..	..	..	1	20	4	80
196–285	10	..	..	..	..	..	..	10	100

Solutions of bilirubin in serum reacted much more slowly than did jaundiced sera having the same color index. The addition of small amounts of disodium phosphate, sodium acetate, or sodium hydroxid accelerated the reaction. In the experiments reported,

disodium phosphate was used to increase the rate of reaction so that it was approximately that observed in jaundiced serum. For this purpose 1 drop of a 10 per cent solution was added to each tube. Since the concentration of sodium phosphate was the same in all tubes the results would not be influenced for the purpose of comparison by this factor. The concentration of sodium hydroxid used in preparing the bilirubin solutions which would have varied with the amount of bilirubin added was likewise made the same in all tubes. The accelerating effect of alkali noticed in these instances has been reported by others (Davies and Dodds;[4] Newman;[13] and Maeda and Morishima[14]) and appears to be related in part to the increased solubility of the added bilirubin, since bilirubin is relatively insoluble at acid reactions, but it is easily soluble in alkaline solutions. The solutions of bilirubin in serum were acid after the addition of the diazo reagent.

Representative data obtained by diazotizing serum solutions containing varying amounts of bilirubin are presented in Table II. The tubes giving immediate and delayed reactions differed only in the quantities of bilirubin each contained. These reactions closely resembled those observed in serum from cases of jaundice.

TABLE II.—EXPERIMENTS WITH BILIRUBIN DISSOLVED IN HUMAN SERUM.

	Icterus index.	Initial color.		Maximum color.		Van den Bergh.
		Min.	Sec.	Min.	Sec.	
Exp. 1	140	0	0	0	40	Immediate.
	75	0	2	0	55	Immediate.
	40	0	5	1	55	Biphasic.
	20	1	5	3	40	Delayed.
	10	1	50	4	30	Delayed.
	3	...	...	8–10	...	Negative.
Exp. 2	140	0	0	0	35	Immediate.
	110	<1	...	1	25	Immediate-biphasic.
	60	<1	...	3	...	Biphasic.
	40	<1	...	4	10	Biphasic.
	18	>1	...	5	20	Delayed.
	12	>5	...	7	...	Negative.
	4	>5	...	10	...	Negative.
Exp. 3	110	0	0	1	30	Immediate-biphasic.
	60	0	20–30	3	5	Biphasic.
	40	0	35–40	4	10	Biphasic.
	18	>1	...	5	20	Delayed.
	12	>1	...	5	30	Delayed.
	6*	3	50	...	...	Delayed.

* Diluting serum gave a delayed reaction.

Dilution Experiments Using Jaundiced Serum. Additional evidence was obtained by diluting serum from severely jaundiced patients with varying quantities of normal human serum. The van den Bergh

reaction and the icterus index were then determined. Typical results are given in Table III. Immediate, biphasic, delayed, and negative reactions occurred in the various dilutions of the same specimen, depending again on the concentration of bilirubin. The results were less clear when dog serum was used because of the increased speed of reaction in this medium. If the dog serum remained in contact with the cells overnight, similar dilutions (freshly prepared) reacted less rapidly. A similar but less noticeable effect of standing was observed when human serum remained in contact with cells for six hours or more. Under these conditions there are changes in the serum which have an inhibiting effect on the van den Bergh reaction. When phosphate buffers were used as diluents all of the reactions continued to be immediate regardless of the dilution.

TABLE III.—DILUTION EXPERIMENTS WITH JAUNDICED SERUM.

Date.	Patient.	Diagnosis.	Dilution.	Icterus index.	Initial color.		Maximum color.		Van den Bergh.
					Min.	Sec.	Min.	Sec.	
April 8	J. S.	Gall-bladder disease	0	45	..	..	..	..	Immediate.
			1:1	20	..	..	..	..	Biphasic.
			1:5	8	1	20	..	..	Delayed.
			1:20	Precipitated by diazo reagent					
Aug. 9	H. S.	...	0	120	..	..	..	..	Immediate.
			1:2	60	..	..	..	..	Immediate.
			1:6	22	..	..	..	..	Biphasic.
			1:30	4	..	..	..	..	Delayed.
Dec. 30	G. B.	Common duct obstruction	0	160	0	2	1	25	Immediate-biphasic.
			3:1	120	0	2	2	..	Immediate-biphasic.
			1:4	35	0	50	4	..	Biphasic.
			1:8	20	1	15	5	10	Delayed.
			1:40	4	5	30	8	..	Negative.
May 28	A. M.	Catarrhal jaundice	0	185	..	..	..	..	Immediate.
			1:20	9	0	20	2	0	Biphasic.
			1:40	4	3	..	..	..	Delayed.
July 10	C. B.	Adenoma of liver, cirrhosis	0	210	0	1	0	30	Immediate.
			1:50	..	0	15–20	2	..	Biphasic.
			1:333	..	3	..	8–10	..	Delayed.
			1:1000	..	5	..	..	..	Negative.
July 25	L. L.	Cholangitis; myelogenous leukemia	0	285	..	..	..	..	Immediate.
			1:7	40	0	20	2	..	Biphasic.
			1:90	3	2	40	3	50	Delayed.

The Effect of Alcohol. The effect of alcohol like that of alkali is to cause a marked increase in the velocity of diazotization of bilirubin in serum. Its action in phosphate buffer solution is similar. This disproves the older explanation of the rôle of alcohol which stated that the increased rate of reaction was due to the liberation

of bilirubin by the alcohol from a hypothetical bilirubin-protein complex. The latter supposedly was characteristic of hemolytic jaundice.

Effect of Temperature. A greater incidence of immediate reactions when the temperature of the laboratory was unusually high suggested an investigation of the effect of temperature on the velocity of diazotization of bilirubin. The marked influence of this factor on the rate of color appearance is shown by experiments made with jaundiced serum. The results are presented in Table IV. The experiments with jaundiced serum and bilirubin dissolved in normal serum were carried out at 20° C.

TABLE IV.—EFFECT OF TEMPERATURE.

1.	Icterus index, 210 Van den Bergh	Temperature, 28° C. Immediate (maximum color, 30 to 40 sec.)	Temperature, 10° C. Biphasic (maximum color, 2 min. 50 sec.)
2.	Icterus index, 17 Van den Bergh	Temperature, 30° C. Biphasic (initial color, 25 sec.)	Temperature, 15° C. Delayed (initial color, 3 min.)

Discussion. The correlation between type of van den Bergh and origin of jaundice has been widely accepted and used as a method for differential diagnosis. Actually the relationship is only incidental to the group differences in concentration of serum bilirubin between jaundice of the hemolytic and obstructive types. In the former there are comparatively moderate changes in serum bilirubin, in the latter much larger increases are common. An examination of a number of cases indicates that hemolytic jaundice when accompanied by marked bilirubinemia gives biphasic rather than delayed reactions. Although immediate reactions have not been observed in this group, neither has there been an instance in which the concentration of serum bilirubin was sufficient to make an immediate reaction probable. On the other hand, delayed reactions frequently occur in mild obstructive jaundice. The type of reaction throughout has been independent of the source of the pigment.

In general, the relationship between icterus index and direct van den Bergh reaction is confirmed in the literature. However, if the indirect van den Bergh reaction is used to determine bilirubin, the velocity-concentration relationship does not hold as well, judging by the results of van den Bergh[1] and Ravdin.[15] The lack of agreement is most conspicuous at higher pigment concentrations where the experimental errors are large.

The effect of changing the medium in which the bilirubin was

dissolved was mentioned in the description of the experimental work. The decrease in the velocity of reaction caused by leaving the diluting serum in contact with the cells probably can be explained by the lowered pH and buffer capacity of the serum treated in this way. The sensitiveness of the reaction to acidity has already been mentioned. Obviously the results of the dilution experiments might be explained by the increasing concentration of an inhibitory substance, and McNee and Keefer[12] state that globulin has an inhibiting action. However, in several experiments freshly prepared serum protein added to jaundiced serum had no effect on the diazo reaction. Furthermore, the correlation of serum color and velocity of diazotization shown in Table I is opposed to such an explanation.

Although there is no valid theoretical basis for the use of the van den Bergh reaction for identifying the various types of jaundice, it remains a useful qualitative test for bilirubin. A clinical survey has substantiated the explanation given by the experimental work.

Summary. The type of direct van den Bergh reaction observed in serum depends upon the concentration of bilirubin.

In the cases here reported an immediate van den Bergh reaction was associated with a high icterus index and a delayed van den Bergh with a low icterus index.

The van den Bergh reaction changed from negative to delayed, then to biphasic, and finally to immediate as increasing amounts of bilirubin were added to human serum.

Dilution of a jaundiced serum with normal serum changed the van den Bergh reaction of the former from immediate to delayed.

The temperature of the reacting materials was shown to be an important factor.

NOTE.—The writers are indebted to Drs. I. S. and E. G. Ravdin for their criticism of the manuscript.

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PRELIMINARY NOTES ON BACTERIOLOGIC STUDIES AND TREATMENT OF CHRONIC EPIDEMIC ENCEPHALITIS.

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Although the etiology of epidemic encephalitis has been the subject of much research during the past ten years, thus far no serious attempt has been made to discover whether there is any relationship between this disease and the Pfeiffer bacillus. It was to determine this relationship that the following work was begun at the Philadelphia General Hospital. For our studies we have chosen cases of chronic epidemic encephalitis; the wealth of clinical material of this type as well as the absence of the fever complicating acute encephalitis—a factor likely to bring out latent agglutinations—determined our choice.

Thus far 165 cases have been studied. Of these 151 present the Parkinsonian syndrome, 7 behavior changes, 5 early Parkinson's with complicating psychoses, one encephalomyelitis and one amyotrophic lateral sclerosis. All available cases of Parkinson's syndrome were studied. No attempt was made to differentiate the encephalitic from the idiopathic or arteriosclerotic types clinically. All were taken regardless of age, previous history of encephalitis, or the presence of advanced arteriosclerosis.

Of these 165 cases, we have complete data on 162. Eighty-four patients gave a history of acute encephalitis, 71 a history of influenza, 60 of these having had this infection in 1918. Twenty-nine gave a history of both acute encephalitis and of influenza and 36 of neither. Two children, one with Parkinson's syndrome and behavior changes, the other with behavior changes alone, gave a history of neither influenza nor of acute encephalitis but their respective mothers had influenza when they were born.

The yearly curve of incidence of acute encephalitis for our cases follows the curve reported by the Matheson Commission[1] except for the fact that our peaks occur in 1920 and 1923 instead of in 1920 and 1924, as they report. For the cases studied, the duration of symptoms of chronic encephalitis was from six months to twelve years. The development of manifestations of chronic disease occurred up to ten years after acute encephalitis and after influenza, if we may assume that this is an antecedent, up to twelve years.

Our control series comprises 122 cases. An attempt was made to have a fair distribution of cases both as to disease and to environment. Thirty-nine were outpatients, the remainder ward patients. Of the latter approximately one-half were patients on an active medical ward, the other half on the rather stationary neurologic ward under the same environmental conditions as the patients suffering from chronic encephalitis.

A history of influenza was elicited from 20 per cent of these control patients. One case had acute epidemic encephalitis in 1921 with apparent complete recovery. Of the neurologic cases 5 were diagnosed multiple sclerosis, 5 Huntington's chorea, 3 Sydenham's chorea, 2 spasmodic torticollis, 2 lenticular degeneration and 5 syphilis, 2 of which had been treated. The remainder consisted of the usual run of cases in wards and clinics.

Bacteriologic Studies. A. *Cultures.* Nasopharyngeal cultures were obtained from 114 cases of chronic epidemic encephalitis and from 37 controls. Two plates were streaked for each case, one of brown-blood agar and one of red-blood agar. The colonies of Pfeiffer bacillus could be studied with ease on the brown-blood plates, while colonies of the other organisms appeared distinctly on the red-blood agar plates. The Pfeiffer bacillus was present in 100 per cent of the nasopharyngeal cultures of patients suffering from chronic epidemic encephalitis and in 46 per cent of the control cases. This latter percentage held for both in- and outpatients. Other organisms found were Streptococcus viridans 63 per cent, Pneumococcus 43 per cent, Micrococcus catarrhalis 38 per cent, Streptococcus hemolyticus 35 per cent, Anhemolytic streptococcus 16 per cent, Staphylococcus 10 per cent, Friedländer's bacillus 5 per cent, Diphtheroids 5 per cent. These organisms showed approximately the same frequency in the cultures both from the experimental series and from the controls.

B. *Serologic Studies.* The agglutination technique followed was according to the method of Evans and Small.[2] A loop of culture of Pfeiffer bacillus was streaked on brown-blood agar plates. The resulting growth was washed off in broth, centrifugalized, resuspended in infusion broth and heated to 85° C. for one hour. The suspension was then standardized to one billion organisms per cubic centimeter. The patient's serum was diluted from 1 to 10 up to 1 to 1280, equal amounts of the suspension was added to these tubes of diluted serum and the tests were incubated in a water bath at 50° C. for eighteen hours. Naked-eye readings were made.

For the flocculation tests, eighteen-hour brown-blood broth cultures were filtered through a Berkefeld filter and the filtrate tested for sterility. Equal amounts of culture filtrate were added to the patient's serum, diluted as for the agglutination tests, and naked-eye readings were made after the tests had stood at room temperature for eighteen hours.

TABLE I.—AGGLUTINATION AND FLOCCULATION REACTIONS IN CHRONIC EPIDEMIC ENCEPHALITIS. (PFEIFFER BACILLUS WAS FOUND IN NASOPHARYNGEAL CULTURES OF ALL CASES.)

(*Hospital of the University of Pennsylvania*)

Name.	Age.	Sex.	Flu.	A. E.	C. E.	Park.	Agg.	Floc.	For. agg.	
P. F.	44	M.	0	0	1927	2	1:20	1:40	B. Mel.	Neg.
H. W.	21	M.	1918	1925	1928	1	1:80	1:80	B. Mel.	Neg.
N. K.	27	F.	0	1920	1920	4	1:20	1:40	S. Vir.	Neg.
D. B.	30	M.	1918	1923	1927	2	1:40	1:40	S. Vir.	Neg.
A. W.	24	M.	0	1924	1924	2	1:160	1:40	S. Vir.	Neg.
E. D.	58	F.	0	0	1927	1	1:80	1:20	S. Vir.	Neg.
W. S.	28	M.	1918	0	1926	2	1:80	1:40	S. Vir.	Neg.
G. S.	46	M.	0	0	1929	1	1:80	1:40	S. Vir.	1:40
A. K.	53	M.	1920	0	1927	2	1:80	1:160	S. C. A.	Neg.
J. S.	14	M.	0	1926	1926	1	1:40	1:80	S. C. A.	Neg.
J. L.	30	M.	0	1920	1920	1	1:40	1:40	S. C. A.	Neg.
L. B.	40	F.	0	0	1926	1	1:80	1:80	S. C. A.	Neg.
W. H.	36	M.	0	1918	1918	1	1:40	1:20	S. C. A.	Neg.
R. S.	42	F.	1921	0	1926	2	1:80	1:40	S. C. A.	Neg.
J. M.	23	M.	0	1928	1928	4	1:40	1:40	S. C. A.	Neg.
P. M.	60	M.	0	0	1929	1	1:80	1:40	S. C. A.	Neg.
C. P.	40	M.	0	1920	1928	1	1:320	1:80	S. C. A.	Neg.
M. H.	37	M.	1918	1920	1928	2	1:80	1:40	S. C. A.	Neg.
E. S.	25	F.	1918	1925	1925	3	1:40	1:40	S. C. A.	Neg.
S. P.	39	M.	1924	0	1926	1	1:40	1:80	S. C. A.	Neg.
V. K.	16	M.	0	1920	1928	4	1:16	1:80	S. Vir.	Neg.
S. G.	47	M.	0	0	1926	1	1:80	1:40	S. Vir.	Neg.
J. S.	40	M.	0	0	1928	2	1:160	1:160	S. C. A.	Neg.
M. R.	22	F.	1918	0	1928	1	1:80	1:40	S. C. A.	Neg.
J. G.	40	M.	0	1924	1924	1	1:80	1:40	S. C. A.	Neg.
H. C.	26	M.	0	1922	1922	1	1:20	1:40	S. C. A.	Neg.
M. C.	38	M.	1918	0	1929	1	1:160	1:160	S. C. A.	Neg.
G. F.	40	M.	0	1928	1928	A.L.S.	1:80	1:40	S. C. A.	Neg.
M. Y.	29	F.	1918	0	1929	E.M.	1:20	1:40	S. C. A.	Neg.
(*Women's College Hospital*)										
M. P.	58	F.	0	0	1929	1	1:20	1:20	S. C. A.	Neg.
W. C	28	F.	1918	0	1929	1	1:40	1:40	S. C. A.	Neg.
H. W.	42	M.	1918	0	1926	2	1:40	1:40	S. C. A.	Neg.
(*Episcopal Hospital*)										
J. K.	46	M.	1918	0	1926	2	1:80	1:80	S. C. A.	Neg.
J. B.	44	M.	0	1925	1925	3	1:20	1:40	S. C. A.	Neg.
M. M.	18	F.	1918	1919	1919	2	1:160	1:160	S. C. A.	Neg.
W. D.	16	M.	0	1923	1923	B	1:160	1:160	S. C. A.	1:80
F. K.	48	F.	1918	1923	1928	2	1:160	1:160	S. C. A.	Neg.
H. P.	41	F.	1926	0	1926	3	1:160	1:160	S. C. A.	Neg.
J. M.	43	M.	1918	1918	1928	3	1:80	1:160	S. C. A.	Neg.
H. K.	24	M.	0	1926	1926	1	1:160	1:40	S. C. A.	Neg.
D. S.	34	F.	1918	0	1928	1	1:320	1:180	S. C. A.	Neg.
G. H.	47	M.	0	0	1928	2	1:320	1:160	S. C. A.	Neg.
H. S.	52	M.	1918	0	1926	2	1:40	1:40	S. C. A.	Neg.
W. D.	18	F.	0	1929	1929	1	1:160	1:40	S. C. A.	Neg.
J. M.	26	M.	1918	1924	1924	3	1:160	1:80	S. C. A.	Neg.
F. G.	43	M.	0	0	1926	2	1:160	1:80	S. C. A.	Neg.
J. D.	30	F.	0	0	1925	1	1:160	1:160	S. C. A.	Neg.

(*Graduate Hospital, University of Pennsylvania*)

Name.	Age.	Sex.	Flu.	A. E.	C. E.	Park.	Agg.	Floc.	For. agg.	
I. D.	24	F.	1918	0	1923	3	1:20			
M. M.	58	M.	1918	0	1929	2	1:80	1:40	B. Mel.	Neg.
M. Z.	21	F.	1918	1918	1927	3	1:40			
E. F.	23	F.	1918	1921	1921	2	1:40			
W. R.	24	M.	0	1920	1926	1	1:80	1:80	S. Vir.	Neg.
R. S.	36	F.	1918	0	1929	3	1:160	1:40	S. Vir.	Neg.
L. S.	39	F.	0	1921	1923	3	1:20	1:20	S. C. A.	Neg.
T. C.	30	M.	0	0	1927	1	1:40	1:160	S. C. A.	Neg.
P. L.	29	M.	1929	0	1929	1	1:40	1:40	S. C. A.	Neg.
B. G.	32	F.	1918	0	1922	3	1:40	1:80	S. C. A.	Neg.
J. R.	29	M.	0	0	1925	2	1:160	1:80	S. C. A.	Neg.
H. J.	31	M.	0	0	1926	3	1:320	1:160	S. C. A.	Neg.
P. L.	13	M.	0	0	1929	1	1:40	1:40	S. C. A.	Neg.
R. Z.	35	M.	0	1923	1929	1	1:20	1:20	S. C. A.	Neg.

(*Miscellaneous Cases*)

N. D.	19	F.	0	1921	1921	4	1:160	1:80	S. Vir.	Neg.
M. L.	24	F.	0	1924	1925	1	1:80	1:80	S. Vir.	Neg.
M. M.	24	F.	1918	1920	1921	4	1:80	1:80	S. C. A.	Neg.
F. R.	49	M.	1918	1921	1921	1	1:80	1:80	S. C. A.	Neg.
S. S.	30	F.	0	1923	1929	1	1:80	1:80	S. C. A.	Neg.
J. W.	70	F.	1918	0	1924	1	1:320	1:80	S. C. A.	Neg.
J. M.	55	M.	1918	1921	1921	2	1:40	1:80	S. C. A.	1:20
A. F.	15	M.	1918	0	1928	2	1:40	1:20	S. C. A.	Neg.
E. B.	38	F.	0	1928	1928	2	1:80	1:40	S. C. A.	Neg.
H. G.	15	M.	1918	0	1926	B	1:160	1:80	S. C. A.	Neg.
M. S.	25	F.	0	1925	1925	1	1:20	1:40	S. C. A.	Neg.
A. R.	24	F.	1918	1925	1925	2	1:80	1:40	S. C. A.	Neg.
A. J.	32	M.	1918	1925	1925	4	1:320	1:80	S. C. A.	Neg.
L. E.	54	F.	1918	0	1928	1	1:40	1:20	S. C. A.	Neg.
M. C.		No	data				1:80	1:80	S. C. A.	Neg.
A.		No	data				1:40	1:40	S. C. A.	Neg.
T.		No	data				1:160			

(*Philadelphia General Hospital*)

R. F.	25	M.	0	0	1923	2	1:40	1:80	S. Vir.	Neg.
F. D.	32	M.	1918	1921	1921	4	1:160			
A. S.	40	M.	0	1923	1924	2	1:80	1:40	S. C. A.	Neg.
S. A.	20	M.	0	1924	1926	4	1:40			
G. C.	38	M.	1920	1920	1924	2	1:80			
H. J.	21	M.	0	1923	1926	4	1:40			
C. P.	22	M.	0	1920	1922	4	1:40	1:40	S. C. A.	Neg.
C. D.	13	M.	0	1919	1921	4	1:320	1:40	S. C. A.	Neg.
C. B.	31	M.	0	0	1922	2	1:40	1:40	S. C. A.	Neg.
W. B.	36	M.	1918	0	1923	4	1:160	1:160	B. Mel.	Neg.
E. D.	43	M.	1921	1921	1926	1	1:80	1:80	S. C. A.	Neg.
A. D.	20	M.	0	1920	1920	4	1:20	1:20	S. C. A.	Neg.
J. F.	24	M.	0	1923	1923	4	1:160	1:60	B. Mel.	Neg.
R. G.	48	M.	1918	0	1928	2	1:80	1:40	S. C. A.	Neg.
G. H.	62	M.	0	1926	1926	2	1:80	1:160	S. C. A.	Neg.
S. T.	24	M.	1918	1921	1921	2	1:160	1:80	S. C. A.	Neg.
G. M.	60	M.	0	0	1918	3	1:40			
M. L.	78	M.	1918	0	1920	3	1:160	1:80	B. Mel.	Neg.

TABLE I.—AGGLUTINATION AND FLOCCULATION REACTIONS IN CHRONIC EPIDEMIC ENCEPHALITIS. (PFEIFFER BACILLUS WAS FOUND IN NASOPHARYNGEAL CULTURES OF ALL CASES.)—(*Continued*)

(*Philadelphia General Hospital*—Continued)

Name.	Age.	Sex.	Flu.	A. E.	C. E.	Park.	Agg.	Floc.	For. agg.	
P. M.	40	M.	0	1926	1928	2	1:80	1:80	S. C. A.	Neg.
A. P.	35	M.	1924	1924	1926	2	1:80	1:80	B. Mel.	Neg.
J. P.	60	M.	0	0	1924	2	1:160	1:80	B. Mel.	Neg.
H. S.	45	M.	1918	1918	1924	4	1:40	1:40	S. C. A.	Neg.
J. T.	51	M.	0	0	1925	2	1:40	1:40	S. C. A.	Neg.
H. E.	24	M.	1918	0	1928	2	1:160	1:80	S. Vir.	Neg.
J. V.	61	M.	0	0	1928	1	1:80	1:80	S. C. A.	Neg.
R. J.	24	M.	0	1929	1929	1	1:20	1:40	S. C. A.	Neg.
C. B.	32	M.	0	0	1928	1	1:160	1:80	S. C. A.	Neg.
A. W.	18	M.	0	1923	1923	2	1:80	1:80	S. C. A.	Neg.
M. K.	45	M.	1918	0	1924	3	1:160	1:80	S. C. A.	Neg.
C. K.	45	M.	0	1924	1927	1	1:80	1:40	S. C. A.	Neg.
P. S.	24	M.	0	1923	1923	2	1:160	1:80	S. C. A.	Neg.
J. M.	25	M.	0	1922	1925	3	1:160	1:40	S. C. A.	Neg.
M. P.	45	M.	0	0	1927	1	1:80	1:160	S. C. A.	Neg.
A. R.	22	M.	1918	0	1927	1	1:40	1:20	S. C. A.	Neg.
J. E.	24	M.	1918	0	1926	2	1:40	1:40	S. C. A.	Neg.
S. S.	55	M.	0	0	1925	2	1:40	1:40	S. C. A.	Neg.
A. F.	28	F.	0	1920	1924	3	1:20			
M. J.	36	F.	0	1921	1924	3	1:640			
A. S.	29	F.	1923	0	1923	2	1:80			
M. B.	48	F.	1921	0	1927	2	1:40			
E. S.	20	F.	1918	1924	1924	3	1:40	1:20	S. Vir.	Neg.
D. E.	31	F.	0	1921	1921	2	1:40	1:80	S. Vir.	Neg.
H. D.	32	F.	0	1923	1923	3	1:20	1:20	S. Vir.	Neg.
M. M.	28	F.	1918	1920	1920	3	1:80	1:40	S. Vir.	Neg.
H. S.	24	F.	1918	1924	1925	2	1:80	1:80	S. Vir.	Neg.
E. P.	19	F.	1918	0	1921	4	1:40	1:80	S. Vir.	Neg.
N. R.	38	F.	0	1923	1926	3	1:40	1:40	S. Vir.	Neg.
J. F.	57	F.	0	0	1924	2	1:80	1:80	S. Vir.	Neg.
M. K.	52	F.	0	0	1920	2	1:160	1:80	S. Vir.	Neg.
F. K.	41	F.	0	0	1921	3	1:80	1:80	S. Vir.	Neg.
S. E.	43	F.	1918	1923	1923	4	1:40	1:40	S. Vir.	Neg.
E. F.	27	F.	1918	0	1921	2	1:80	1:80	S. C. A.	Neg.
S. D.	68	F.	0	0	1920	4	1:160	1:80	S. C. A.	Neg.
R. T.	62	F.	0	0	1928	1	1:80	1:160	S. C. A.	Neg.
E. B.	35	F.	1918	0	1925	3	1:80	1:80	S. C. A.	Neg.
J. E.	61	F.	0	0	1928	4	1:40	1:80	S. C. A.	Neg.
N. H.	50	F.	1918	0	1928	1	1:80	1:80	S. C. A.	Neg.
M. F.	29	F.	0	1919	1927	2	1:80	1:20	S. C. A.	Neg.
L. S.	26	F.	1918	0	1926	1	1:40	1:80	S. C. A.	Neg.
J. S.	15	F.	0	1925	1925	1	1:80	1:80	S. C. A.	Neg.
C. L.	16	F.	0	1925	1928	1	1:160	1:80	S. C. A.	Neg.
A. P.	23	F.	0	0	1923	2	1:80	1:80	S. C. A.	Neg.
G. H.	30	F.	1918	1924	1925	2	1:40	1:20	S. C. A.	Neg.
J. M.	25	F.	1918	0	1925	1	1:40	1:40	S. C. A.	Neg.
A. C.	55	F.	1924	1924	1924	3	1:80	1:80	S. C. A.	Neg.
M. S.	26	F.	0	0	1928	3	1:80	1:80	S. C. A.	Neg.
F. A.	21	F.	1918	0	1929	1	1:80	1:80	S. C. A.	Neg.
M. M.	24	F.	0	1923	1926	2	1:320	1:160	S. C. A.	Neg.
A. G.	42	F.	0	0	1925	3	1:160	1:80	S. C. A.	Neg.
M. C.	28	F.	1918	1925	1925	1	1:80	1:80	S. C. A.	Neg.
A. H.	40	F.	1918	1919	1919	2	1:160	1:160	S. C. A.	Neg.
C. F.	20	F.	1918	1925	1928	1	1:80	1:40	S. C. A.	Neg.
A. J.	30	M.	0	0	1926	1	1:80	1:40	S. C. A.	Neg.
H. S.	70	M.	0	1920	1920	4	1:320	1:160	S. C. A.	Neg.
M. K.	24	M.	1918	0	1918	2	1:40	1:40	B. Mel.	Neg.

(*Philadelphia General Hospital*—Continued)

Name.	Age.	Sex.	Flu.	A. E.	C. E.	Park.	Agg.	Floc.	For. agg.	
N. K.	20	M.	0	0	1918	2	1:40	1:40	B. Mel.	Neg.
T. F.	25	M.	1918	0	1928	Psy.	1:40	1:80	S. C. A.	Neg.
T. K.	39	M.	0	1919	1926	Psy.	1:40	1:20	S. C. A.	Neg.
A. B.	16	M.	0	0	1929	Psy.	1:20	1:20	S. C. A.	Neg.
A. G.	46	M.	0	1928	1928	Psy.	1:40	1:20	S. C. A.	Neg.
T. E.	20	M.	1918	0	1928	Psy.	1:80	1:80	S. C. A.	Neg.
H. B.	29	M.	0	1924	1924	2	1:160	1:40	S. C. A. P. G. H.	Neg.
				CHILDREN.						
S. B.	9	M.	0	1922	1922	B	1:160	1:40	S. C. A.	Neg.
R. M.	6	F.	0	1928	1928	B	1:320			
J. H.	6	M.	0	1929	1929	B	1:320			
R. S.	9	F.	0	?	1926	B	1:20	1:40	S. C. A.	Neg.
E. E.	11	M.	Flu	during	preg.	B	1:20	1:20	S. C. A.	Neg.
M. G.	6	M.	Flu	during	preg.	B	1:80	1:80	S. C. A.	Neg.

KEY.

A. E. = Acute epidemic encephalitis.
C. E. = Chronic epidemic encephalitis.
Agg. = Agglutination.
Floc. = Flocculation.
For. agg. = Foreign agglutination.
Park. = Parkinsonian syndrome. 1, Mild Parkinsonism. 2, Moderate. 3, Severe. 4, Very advanced.
B. = Behavior changes.
A. L. S. = Amyotrophic lateral sclerosis.
E. M. = Encephalomyelitis.
S. C. A. = Streptococcus cardioarthritidis.
S. Vir. = Streptococcus viridans.
B. Mel. = Bacillus melitensis abortus.
Psy. = Parkinsonism with psychosis.

Agglutination tests were performed with 165 chronic encephalitic sera. These tests were positive with the Hammett[3] strain of the Pfeiffer bacillus in 100 per cent, the agglutination titers ranging from 1 to 20 to 1 to 640, while the flocculation titers ranged from 1 to 20 to 1 to 160. There seemed to be no correlation between either the duration or the severity of the disease and the degree of agglutination titers. Neither were there higher readings in cases giving a history of acute encephalitis and influenza than in cases giving negative histories. Of the entire series 8.6 per cent agglutinated the Hammett strain in a titer of 1 to 20, 28.2 per cent agglutinated in a titer of 1 to 40, 34 per cent in a titer 1 to 80—22 per cent in a titer 1 to 160—6 per cent in a titer 1 to 320 and 0.6 per cent in a titer of 1 to 640.

Since it could be argued that other organisms might also be agglutinated by the sera of these patients, we purposely tested the sera of 148 of these patients against one of three other organisms, namely, Anhemolytic streptococcus, Streptococcus viridans and Bacillus melitensis abortus. These tests were set up simultaneously with the Pfeiffer agglutinations and flocculations. Three of these sera agglutinated Anhemolytic streptococcus and one Streptococcus viridans.

Of 122 control cases only 3 afebrile cases showed agglutinations with the Pfeiffer bacillus. One was a patient with central nervous system syphilis (1 to 80); another a patient diagnosed lenticular degeneration whose symptoms—choreiform movements—dated from 1912, when at the age of one year, he had an undiagnosed febrile condition followed by great restlessness (1 to 40); and the third, a patient suffering from bronchiectasis and asthma from whom the Pfeiffer bacillus was constantly obtained in bronchial cultures (1 to 20). A recovered case of influenzal meningitis did not agglutinate, but showed flocculation with the Pfeiffer bacillus.

Four cases with marked hyperpyrexia also agglutinated the Pfeiffer bacillus in titers of 1 to 20 to 1 to 80. One of these cases also agglutinated Bacillus melitensis abortus, one Anhemolytic streptococcus and 2 Bacillus typhosus. The other 110 cases gave negative agglutination and flocculation reactions with the Hammett strain of the Pfeiffer bacillus. Of 10 undiagnosed patients examined for Dr. F. Burge of Philadelphia, 4 gave positive agglutinations and 6 negative reactions. These cases have not been listed as they cannot be classified.

In further culture studies the Pfeiffer bacillus was isolated from the throats of chronic encephalitic patients in pure culture. Antigens were made from these strains by the method before described. In 18 cases the strain of Pfeiffer bacillus isolated from the patient's nasopharynx was agglutinated by the homologous serum in dilutions from 1 to 40 to 1 to 2560. The titers of the homologous agglutinations were higher than when the Hammett antigen was used against the same sera. These 18 encephalitic antigens were also agglutinated by the Hammett immune horse serum: the agglutination titers thus obtained ranging from 1 to 40 up to 1 to 2560. Not in all cases was the agglutination with the Hammett immune serum as high as that with the homologous serum, but there was an indication of subgrouping serologically. Further work will be carried out upon this particular phase of the problem as it appears most suggestive.

Experimental work with animals is contemplated in order to determine whether or not there is a serologic relationship among the strains of Pfeiffer bacillus isolated from patients suffering with chronic epidemic encephalitis. Another group of animals will be sensitized to these same strains in order to determine whether there is a protein common to these strains.

Treatment. At the present time 62 patients suffering with chronic epidemic encephalitis are being treated with the bacteriologic products of the Hammett strain of the Pfeiffer bacillus. These products are the immune horse serum, the soluble antigen and the vaccine.

The horse serum is prepared by immunizing the animal against the Hammett strain of the Pfeiffer bacillus. The vaccine is made

in the usual manner but the organisms killed with thymol. The following technique is used in the preparation of the soluble antigen. Cultures of the Hammett strain of the Pfeiffer bacillus are streaked on brown-blood plates and incubated overnight at 37.5° C.; the resulting growth is washed from the plates with sterile physiologic salt solution and the heavy particles allowed to settle to the bottom of the tube. Two washings are made of the supernatant fluid. The organisms are heat killed at 60° C. for one hour and resuspended in a dilution of one hundred million organisms per cubic centimeter and allowed to stand at icebox temperature for one week. This suspension is then passed through a Grade A Berkefeld filter, and tested for sterility. The resulting water-clear filtrate is then diluted 1 to 10,000 for clinical use. This method is very similar to the one used by J. C. Small in his preparation of the soluble S.C.A. antigen, the only difference being in the original method of growth and treatment of the organisms.

We feel justified in using a soluble antigen of a virulent strain of Pfeiffer bacillus in the treatment of these cases, since it has been found by mouse experimentation that toxins from virulent strains of the Pfeiffer bacillus although of dissimilar serologic relationship, were neutralized by the same immune antiserum. This work will be further discussed in a future paper. This observation finds a parallelism in diphtheria toxins where, although there are several serologic strains, all are neutralized by the same antitoxin. It is upon this basis that we use the Hammett soluble antigen, for although it was not isolated from a case of chronic encephalitis, it is a most virulent strain.

Sixteen cases were treated with the immune serum. Of these 7 showed serum reactions with fever and urticaria. There was some improvement in approximately one-third of these cases but this is not sufficient to claim specificity. It could well have been the result of nonspecific protein reaction.

Since the patients treated with soluble antigen showed as much improvement as those treated with serum and antigen and more than those treated with serum alone, the use of the serum has been discontinued in chronic manifestations of the disease, these cases being treated with the soluble antigen.

It has been found that 0.1 cc. of a 1 to 10,000 dilution of the soluble antigen every five to seven days gives best results. Improvement under this treatment consists in reduction of the extrapyramidal rigidity which, is the most constant finding in this disease and is the cause of its most important symptoms and signs. The patient gradually feels less stiff, regains the use of his arms and legs, the posture becomes more erect, there is a decrease in festination, the face becomes more mobile and the speech less monotonous. The first symptom of improvement noted in early cases of this disease is decrease in slowness. It is an interesting observation that as the

extrapyramidal rigidity decreases, tremor concomitantly increases. This can be explained upon a purely mechanical basis.

Increasing doses of the soluble antigen aggravate rather than relieve the symptoms. There is however no febrile reaction. In one patient who showed decrease in rigidity with repeated doses of 0.1 cc. of 1 to 10,000 dilution of the antigen, the dose was increased to 0.4 cc. Her rigidity was increased by this dose to such an extent that she could hardly return to clinic. This phenomenon has been repeated in several instances.

But little improvement is noted in less than one month of treatment. Therefore we shall report only those cases which have been treated for this period or longer. Of these there are 46 cases, 34 of which show definite improvement. Of the patients with Parkinson's syndrome 78 per cent have shown a definite decrease in extrapyramidal rigidity. Subjectively there is a sense of greater mobility and the patient is able to get about better than before. It is most difficult to determine improvement in behavior cases. The environment of these patients has not been sufficiently controlled to make such observations valid.

We have been forced to give hyoscin and stramonium to about 20 per cent of our cases to enable them to get to the clinic. Our technique has been to allow our patients to continue with the same dosage of drugs that they were taking before they received their first dose of soluble antigen. This dose is then reduced as the antigen treatment progresses. Several patients who were taking $\frac{1}{100}$ gr. of hyoscin three times daily have had this drug entirely withdrawn and now are better than they were while taking it.

We expect to treat an adequately controlled series of cases of chronic epidemic encephalitis with this soluble antigen on the wards. Our results then will not be vitiated by the use of drugs. We also intend to treat a series of controls with the same dosage of the soluble antigens of other organisms.

It is logical to believe that there is a focus of infection in these cases. Since the Pfeiffer bacillus is invariably isolated from nasopharyngeal cultures, the upper respiratory tracts of these patients are being carefully investigated. Thus far 20 of our cases have had both Roentgen ray studies of the accessory sinuses of the nose, and examination by a laryngologist. Eighteen cases show evidence of definite sinus involvement either by Roentgen ray or clinical examination. Of these, 13 cases have disease of the ethmoids. Deflected septum with blocking of the nasal passage is a common finding and cultures of the middle meatus of the nose reveal the presence of the Pfeiffer bacillus in 80 per cent of such cases.

A group of these patients will be treated with a course of Pfeiffer vaccine and local application of Besredka filtrate along with any mechanical interference indicated to clear up the sinuses.

The fact that the patients improve on constant minute doses of

the soluble antigen, however, suggests that we are dealing also with a sensitization. There is need for further investigation along these lines. We consider however that our results are not due to nonspecific protein reaction, since the usual dose of antigen contains only .000,000,000,094 gr. of protein.

Summary. 1. The Pfeiffer bacillus was isolated from nasopharyngeal cultures of chronic encephalitic patients in 100 per cent of cases.

2. The sera of chronic encephalitic patients agglutinated the Hammett strain of the Pfeiffer bacillus in 100 per cent of cases studied. Flocculation tests were also invariably positive with these sera. No other organism thus far tested has been consistently agglutinated by chronic encephalitic sera.

3. Cultures of the Pfeiffer bacillus isolated from 18 cases of chronic encephalitics agglutinated their respective patients' sera and also agglutinated the Hammett strain of Pfeiffer bacillus immune serum. The agglutination with the Hammett immune sera was not so high as that of the homologous patient's sera but suggested the existence of a serologic subgrouping.

4. Of the control series: (*a*) Pfeiffer bacillus was isolated in 46 per cent of nasopharyngeal cultures; (*b*) 122 nonencephalitic sera were tested for agglutination. Of these, 114 neither agglutinated nor flocculated the Pfeiffer bacillus.

Of the 7 control cases that agglutinated the Pfeiffer bacillus 3 were afebrile, a case of syphilis of the central nervous system, a lenticular degeneration with a questionable history and a patient proved to be sensitive to the Pfeiffer bacillus. Four febrile cases agglutinated the Pfeiffer bacillus but also agglutinated other organisms.

5. Of 20 cases of chronic encephalitic Parkinsonism studied for sinus disease, 18 gave positive findings either by Roentgen ray or clinical examination; 13 of these had definite disease of the ethmoids.

6. Of 46 cases of chronic encephalitic Parkinson's disease treated for one month or more with the soluble antigen, 78 per cent show improvement. This is considered as not due to a nonspecific protein reaction, since the dose of antigen given contains only ninety-four ten-billionths of a gram (.000,000,000,094) of protein.

NOTE.—We wish to extend our thanks to the neurologists at the Hospital of the University of Pennsylvania, the Philadelphia General, the Graduate and Episcopal Hospitals for permitting us to study their patients and to Dr. A. S. W. Rosenbach, whose generosity has furthered this work.

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THE FUTILITY OF ALKALI TREATMENT IN DIABETIC COMA.

Analysis of Forty-seven Cases.*

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The present series is presented as corroborative evidence in support of Joslin's contention that the use of alkalies in diabetic coma is unnecessary. While his experience in a series of 105 cases is convincing, it seems desirable to gather as large a number of coma cases treated without alkalies and as from as many sources as possible. In spite of the flood of papers concerning insulin in the past seven years, there are relatively few recorded series of coma cases from which conclusions may be drawn. Table I gives all such series with more than 20 cases.

While Joslin[1] enumerates Petren, the Minkowski school, Falta, Priesel and Wagner, Newburgh and Marsh, Bertnard Smith and many others as having given up the use of alkalies, there still remains an uneasy feeling in the minds of many that the antiketogenic effect of insulin may not be sufficient nor prompt enough and that its effect upon the alkali reserve may be inadequate to offset the acidosis caused by other possible acid bodies. I have recently had an opportunity to review the records of 49 cases of coma treated by a number of different men in a certain hospital in the past five years. In 25 of these alkalies had been used. Meyer-Bisch[2] in 1926, in attributing the symptoms of diabetic coma to concentration of the blood and to hypochloremia, reported 4 cases of coma in which the intravenous injection of soda bicarbonate solution restored the patients to consciousness within a few minutes, whereas the coma had continued after insulin (in one case where the blood sugar had fallen to 80 mg. per 100 cc. and where "hypoglycemic twitchings" had appeared). Hédon[3] reported that his depancreatized dog brought into diabetic coma by the sudden withdrawal of insulin was restored instantly to consciousness by intravenous soda bicarbonate solution whereas the reinauguration of insulin therapy caused the disappearance of the glycosuria, hyperglycemia and diaceturia but had not brought about the restoration of consciousness. Such experiences might serve to reinforce the feeling of some that soda bicarbonate should supplement the effect of insulin. The suggestion of Bock[4] and Starr and Fitz[5] that there may be acting in coma, acid bodies other than ketone bodies is held to be an additional reason for the employment of alkalies. In this connection we may ask, Do the

* Read at the meeting of the Association of American Physicians. Atlantic City, May 7, 1930.

ketone bodies act as specific poisons or merely as any other acids might? The question of the pathogenesis of diabetic coma has not been solved in spite of the long controversy and of the numerous researches.

TABLE I.—SERIES OF COMAS REPORTED IN LITERATURE DURING INSULIN ERA.

Author.	Cases of coma.	No. of deaths.	Died (%).	Year.	Remarks.
1. Foster: J. Am. Med. Assn., **84**, 719	20	2	10	1925	No statement as to use of alkalies.
2. Kahn and Olmsted: J. Met. Res., **7**, 29	24	3	12.5	1925	All deaths in cases with complications. Total series, 25; 1 omitted because death due to no insulin being available. Soda was used.
3. Violin: Wien. klin. Wchnschr., **39**, 1304	21	5	24	1926	No statement as to use of alkalies.
4. Leake: Calif. and West. Med., **26**, 475	53	37	70	1927	27 had grave complications. Soda used.
5. Chabanier, *et al.*: Presse méd., **1**, 83	28	2	7.1	1927	No soda.
6. Petren: Verhand. d. deutsch. Kong. f. inn. Med., **39**, 203	72	4.1*	5.5	1927	* Including 1 death apparently from pneumonia. No soda.
7. Elias: Wien. med. Fakult, No. 95 .	42	..	24	1924–1925	Quoted by H. J. John.
8. John, H. J.: J. Am. Med. Assn., **93**, 425 . . .	71	4	5.6	1929	Insignificant quantities of Bisodol used by mouth.
9. Joslin, E. P.: Med. Clin. N. Am., **13**, 11	105	7	6.6	1929	7 deaths during coma, 2 from uncomplicated coma, 5 from complications with coma; 7 more recovered from coma but died in hospital from complications in from 6 to 31 days. No alkalies used
10. Blackfan . . .	21	0	0	1929	Quoted by Joslin (9); 1 patient received alkalies.
11. Lemann: Present series	47	5	10.6	1930	2 deaths within 2 hours of admission; 1 death with complicating chronic nephritis.
12. Lemann: Present series; cases without alkali . . .	41	3	7.3	1930	If 2 patients who died within 2 hours are omitted, net mortality is 2.4 per cent.

It is striking that insulin acts not only as a specific antidote to the ketone bodies but also by raising the soda bicarbonate content of the blood and tissues sometimes even to the point of causing a

definite and menacing alkalosis; so that whether we adopt the acid intoxication theory or the specific intoxication theory, insulin might be by itself theoretically regarded as sufficient. The argument in favor of insulin without reinforcement of alkalies is strengthened not only by the consideration of its production of alkalosis but also by its action in those cases of diabetic coma without the appearance of ketonuria. In these latter cases the failure of the ketone bodies to appear in the urine has been attributed to kidney block caused either by the coma, or rather its specific cause, or by a concomitant or previously existing nephritis. In such cases, therefore, we are dealing not only with the acidotic or specific effect of the ketone bodies but also with the effect of other acidotic material retained in the body because of the inability of the damaged kidney to excrete it. The effect of insulin, therefore, in rescuing such diabetic-coma patients who do not exhibit ketonuria is additional evidence of its adequacy even where we have to concede the theoretic need of combating acidosis arising from sources other than the ketone bodies. I have previously[6] reported the details of the rescue of such patients with insulin only and these cases are included in the present series.

The relation of the degree of the impairment of the alkali reserve to the depth of the coma is of interest and perhaps importance in considering the rôle of alkali therapy. I have found, like Joslin, that the degree of coma is not proportional to the blood CO_2 level. The most profound coma was not always characterized by the lowest CO_2 combining power of the blood plasma nor on the other hand was the lowest CO_2 value accompanied by the deepest coma. Should this be regarded as evidence against the acid intoxication theory and in favor of the specific ketone intoxication theory of the pathogenesis of diabetic coma? I have observed recovery from coma usually running parallel to the rise in the CO_2 combining power of the blood plasma and the disappearance of the ketonuria. This is apparently not in accordance with Joslin's experience.[7]

The present report covers 47 comas in 34 patients. Not all of these patients were completely unconscious. Some of those retaining consciousness to a certain degree at least exhibited, as I have said, the lowest CO_2 combining power. Where complete coma was not present, the diagnosis of "diabetic coma" was justified on the basis of the Kussmaul air hunger, the clouded sensorium and the low CO_2 combining power. The lowest CO_2 combining power was 6.6 volume per cent. The highest blood-sugar reading was 1204 mg. per 100 cc. Both of these patients were rescued. Included in this series also are 2 patients whose urine showed no diacetic acid at the time of the coma. One of these patients had congestive heart failure, showed auricular fibrillation at the time of her coma and subsequently died of heart and kidney disease many months after the diabetic coma. The other patient proved also to have evidence of chronic kidney disease. I saw her first when she had been completely unconscious for more than twelve hours. Intravenous infusion of

soda bicarbonate by her attending physician twelve hours before my first visit had produced no effect whatsoever. She was rescued then by insulin alone and without further alkalies. In a second coma she was again rescued without alkalies. In the third coma, in which she died, soda bicarbonate intravenously was again used in addition to the insulin but without affecting the clinical picture. Unfortunately no autopsy was permitted. The experience in the four comas seen in these 2 patients would lead one to believe that insulin alone and without alkalies is effective and adequate to combat the acidosis caused by hypothetic other acid bodies when chronic kidney disease exists as a complication of diabetes.

Allusion may also be made here to the acute kidney block produced apparently by the diabetic coma itself. In the case for example of the patient with the blood sugar of 1204 mg. per 100 cc. there was much evidence of such a condition. The urine showed many hyaline, granular and finely granular casts, red blood cells and pus cells. The relation of the kidney block to the level of the blood chemistry and to the CO_2 combining power is shown in Table II. It will be noted that the retention of nitrogen persisted after the patient had been restored to consciousness and the CO_2 combining power approached normal. At the end of the first month the total nonprotein nitrogen of the blood was 30 mg. per 100 cc. and there was no evidence of any nephritis. It is common to find that all the evidences of severe nephritis clear up when the patient recovers from the diabetic coma. The point to be made here again is that insulin alone is sufficient to combat such hypothetic acidosis as may be attributed to the acute kidney involvement and not regarded as essentially diabetic (ketogenic).

TABLE II.—RELATION OF KIDNEY BLOCK TO THE LEVEL OF BLOOD CHEMISTRY AND TO THE CO_2 COMBINING POWER.

Blood sugar.	Total nonprotein nitrogen.	Creatinin.	Uric acid.	CO_2 combining power.	Remarks.
1204	60	3.11	8	9	
500	75	3	10	31	380 units of insulin to this point—end of first 24 hours.
325	100	3.11	8.8	37.4	End of second 24 hours.
258	100	3	8	36.5	End of third 24 hours.
103	88.8	2.3	6.64		End of fifth 24 hours.

The 47 comas in the 34 patients were complicated by serious conditions in 14 comas.

1. Abscess of the gluteal region. Patient recovered. No. 3033.
2. Abscess of the gluteal region, tuberculosis of the breast. Patient recovered. No. 2898.
3. Perirectal abscess. Patient recovered. No. 1953.
4. Otitis media. Patient recovered. No. 1972.

5. Otitis media. Patient recovered. No. 2898.
6. Organic heart and kidney disease. Patient recovered. No. 2374.
7, 8, 9. Chronic kidney disease. Patient recovered from the first and second comas but died in the third. No. 2021.
10. Pyelonephritis. Patient recovered. No. 2367.
11. Septicemia, bronchopneumonia and pyelonephritis. Patient recovered from the coma but died nearly a month later from the septicemia and pyelonephritis. No. 1898.
12. Alveolar abscess. Patient recovered. No. 3035.
13. Multiple large carbuncles. Patient recovered. No. 2146.
14. Large carbuncle of the neck. Patient died within two hours of admission. No. 2389.

It will be observed, therefore, that serious complications and infections did not produce an acidosis which could not be successfully combated with insulin alone and without alkalies.

The age of the patients was below ten years in 3 comas, between ten and twenty years in 16 comas and over twenty years in 28 comas.

There were 5 deaths in this series of 47 comas—a mortality of a little more than 10 per cent. Two patients died within two hours of their admission. One of the other deaths was certainly due to insufficient insulin; it occurred in the early insulin days, before an adequate supply was available. Another death was possibly due also to insufficient insulin for I would now consider the amount used (150 units in fifteen hours) inadequate. Soda bicarbonate was used in only 6 instances—all in the early insulin days and always in very small amounts—4 gm. (200 cc. of 2 per cent solution). One of the 6 instances is represented by the patient who died because of inadequate supply of insulin. Two other instances were represented by the first and third comas of the patient with chronic nephritis without ketonuria.

Forty-one comas, therefore, were treated with insulin alone without alkali. In this consecutive series there were 3 deaths, namely, 2 patients who died within two hours of their admission and the patient who received 150 units of insulin in fifteen hours. If we omit the 2 patients dying within two hours of their admission we have one death in 41 comas or a net mortality of 2.4 per cent, even in the presence of grave complications.

The case against alkalies can, therefore, be stated exactly as Joslin has put it—first, they are unnecessary, second, they may do harm. It is hardly necessary to refer to the futility of alkalies alone before the insulin era. As Olav Hanssen[8] has written "the coma patients who have been rescued by this treatment are so few that their number can certainly be written down in single numerals." St. Lorant[9] saved one out of 42 coma cases in the preinsulin era. The one was saved by rupture of the ear drum relieving an acute middle-ear abscess. All the others had had great quantities of alkalies. Hanssen found that in 3 out of 6 cases treated with intravenous injections of sodium bicarbonate solutions convulsions occurred. In the postmortem examinations of the brains in all of

the patients treated with sodium bicarbonate there was found intense hyperemia and edema in the thin meninges. In 5 cases there were small flakelike hemorrhages in the meninges and in 2 cases there were small hemorrhages in the brain substance. Even those who at first advocated the use of soda bicarbonate intravenously as an adjunct to insulin therapy in coma have retreated and agree that[10] "undoubtedly too much alkali will kill and undoubtedly alkali intravenously administered is exceedingly dangerous and should rarely be employed even by those highly skilled in its administration." Some still contend that soda bicarbonate in amounts of 20 to 30 gm. is a useful addition to the treatment of diabetic coma. The usefulness of these small doses may be questioned in the light of the calculation that from 100 to 200 gm. would be required to neutralize the amount of the ketone bodies found in the urine of coma patients.[8] Why give any if insufficient amounts are given and if it can be shown that none is needed? Recent literature contains reports of alkalosis caused by therapeutic doses of alkali in the treatment of gastric and duodenal ulcer.[11] With even small amounts given by mouth or rectum care must "be exercised that the alkali concentration of a liquid does not cause its rejection."[10] This caution is by no means based on theoretical considerations. The retention of fluids by the desiccated coma patients is of much greater importance than any questionable good of small doses of alkali.

Conclusion. No indication nor excuse for the use of alkali therapy to supplement insulin was found in the depth of the coma, in duration before the institution of treatment, in the maximum grade of glycemia, the lowest value of CO_2 combining power of the blood plasma, in grave complications, nor in kidney block nor concomitant chronic nephritis. Soda can do no good and can do harm.

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REVIEWS.

SURGERY OF THE LUNG AND PLEURA. By H. MORRISTON DAVIES, M.A., M.D., M.CH. (CANTAB.), F.R.C.S. (ENGLAND). Pp. 355; 104 illustrations. New York: Oxford University Press, 1930.

THERE has been a most noticeable advance in the surgery of the chest during the last ten years. Sauerbruch, in Germany, and Lilienthal, in America, have given excellent treatises on intrathoracic surgery, but this present work compares most favorably with theirs. The writer has drawn freely on the literature as well as his own experience, which latter has been most extensive. This is especially true of the chapters on tuberculosis, which are valuable alike for their diagnostic acumen and their surgical wisdom, because of the writer's past experience and long training in sanatorium work. The entire subject is covered. Chapters deal fully with the anatomy, physiology, diagnosis, pathology and treatment of disease and injury of the thorax and its contents. The text is supplemented by numerous well-chosen and excellently reproduced illustrations, chiefly drawn from the writer's own case histories. A very full bibliography is added as a last chapter of this most instructive and up-to-date contribution.

E. E.

THE HARVEY LECTURES, SERIES XXIV, 1928–1929. Pp. 216; 36 illustrations. Baltimore: The Williams & Wilkins Company, 1930.

THE Harvey Lectures for 1928–1929 maintain their customary high level. The following lectures were given: "Senescence and Rejuvenescence from a Biologic Standpoint," by C. M. Child; "The Nature of the Ultrafilterable Viruses," by F. d'Herelle; "The Metallotherapy of the Spirochætoses," by C. Levaditi; "Urine Formation During the Acute and Chronic Nephritis Induced by Uranium Nitrate," by William de B. MacNider; "Constitutional Variation and Susceptibility to Disease," by Wade H. Brown; "Calcium and Phosphorus Metabolism," by Joseph C. Aub; "The Biochemical Digitalis Problems," by Walther Straub; "The Pathogenesis and Transmission of Tuberculosis," by Eugene L. Opie.

E. K.

PEPTIC ULCER. By JACOB BUCKSTEIN, M.D. Vol. X of *Annals of Roentgenology*. Edited by JAMES T. CASE, M.D. Pp. 337; 287 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, $12.00.

THIS monograph is one of the series of annals published by Paul B. Hoeber, and it deals with the roentgenologic aspects of peptic ulcer. The author has briefly considered the types of stomachs, and the various types of gastric mucosa. He also discusses briefly the various types of ulcers of the stomach and duodenum, and he includes two illustrations of ulcers of the esophagus. The pathology of the lesions found at operation are correlated with the roentgenologic findings. Included is some excellent work on the roentgenographic findings of ruptured peptic ulcers, jejunal ulcers and gastrocolic fistulas resulting from marginal ulcers.

The subject is presented in a concrete and excellent manner. The print and illustrations are excellent. The roentgenologic findings are correlated with the operative and pathologic findings, and this makes the book more valuable. It should be of interest to all roentgenologists. E. P.

THE TREATMENT OF SKIN DISEASES IN DETAIL. By NOXON TOOMEY, M.D. Pp. 512. St. Louis: The Lister Medical Press, 1930. Price, $7.50.

THIS is apparently the third volume of a system, of which the first two volumes are yet to appear. Like all texts dealing with dermatologic subjects, it presents features both to admire and condemn. The book is without illustrations, which is an interesting departure, and contains valuable detail as to the makeup and application of medicinal preparations which is frequently omitted from the average practitioners' handbook. The attempt to reclassify certain aspects of dermatology results in the addition of a number of new, not particularly useful and rather cumbersome names to an already overloaded nomenclature. A genuine effort is made to present the constitutional background of certain dermatoses but the product still retains the unmistakable flavor of empiricism that continues to mark even the best dermatologic practice. Considering that dermatology differentiates itself sharply into procedure which should be available to the practitioner and procedure which he should never attempt, it is probably too much to expect that any inclusive text will ever wholly satisfy both groups. It is noticeable that the author subscribes to the use of Roentgen ray in the removal of excessive hair growth, a procedure which, no matter how carefully guarded technically, does not have the general acceptance of dermatologists either in this country or abroad. On the

other hand, the book contains items of detail of the greatest interest to the practising dermatologist. For example, this is the only text in which the Reviewer has noted sufficient attention to the question of qualified results in hair removal and the only one emphasizing a genuine knowledge of dietotherapy. One turns from the work with a feeling that this is a very creditable effort to bring dermatologic practice down to the detail which is of its essence, but that it has not yet accomplished what another generation may do for us—the adequate textbook presentation of a rational dermatologic treatment.

J. S.

TONSIL SURGERY. By ROBERT H. FOWLER, M.D. Pp. 288; 103 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $10.00.

AUGMENTED by splendid illustrations, this book describes in great detail the anatomy and surgery of the faucial tonsil. The details of the technique of the tonsil operation as carried out in eight different clinics, are presented. The author and coworkers deserve particular praise for their original work on the anatomy of this region. It is unfortunate that one of the methods advocates the injection of cocain solution for the purpose of local anesthesia (page 104). In the present era of safer local anesthesia it seems dangerous to present the above procedure as representative, for certainly almost all surgeons agree that under no circumstances should cocain be injected. With the above reservation, this book is recommended to the throat surgeon, especially the young man who wishes to crystallize his ideas and develop his technique for thorough, yet safe, tonsil surgery.

K. H.

TRAUMA, DISEASE, COMPENSATION. By A. J. FRASER, M.D. Pp. 524. Philadelphia: F. A. Davis Company, 1930. Price, $6.50.

THE author has made a study of Workmen's Compensation and has here set down a compilation of cases and facts which may be used by those dealing in compensation and industrial insurance. The first chapter concerns the basis and scope of Workmen's Compensation and cases are cited defining the various provisions of the act. Various parts of the body are then discussed in detail and examples and authorities are given to show how the diseases under discussion may or may not be compensable. The chapters on fracture and hernia are good but the author has avoided one of the commonest industrial diseases, traumatic backache.

The book is evidently intended for use by the laity since a glossary is attached. Because the author is a Canadian a greater part of the authorities quoted and the opinions given come from British or Canadian literature, and some of the cases may not be applicable for use in the United States. However, it should prove useful to those dealing with compensation insurance and industrial medicine.

L. F.

DIE REGULIERUNG DES BLUTKREISLAUFES. By DR. W. R. HESS. Pp. 163; 21 illustrations. Leipzig: Georg Thieme, 1930. Price, M. 12.

THE author has succeeded in the stupendous task of covering the extremely large literature on this subject with great thoroughness. A list of 703 references are given even though prolific writers are usually referred to through review articles or books (for example, T. Lewis is cited in a single reference only). The monograph will consequently prove of very great value to all workers in this and related subjects. Often 20 to 40 references are made in the course of a single page; this increases the value of the book as a guide to the study of the literature, but prevents to some extent the development of the material discussed in any detail in the monograph itself.

The author has succeeded surprisingly well in keeping the references up to date and many references to articles published in 1929 are included.

The subjects dealt with are: (1) Regulatory functions of the capillaries; (2) regulation of the arterial bloodflow; (3) rôle of veins in regulation of the circulation; (4) rôle of the spleen in regulation of the circulation; (5) regulation of cardiac activity; (6) regulatory coördination of the organs concerned with the circulation.

H. B.

TUBERCULOSIS AMONG CHILDREN. By J. ARTHUR MYERS, PH.D., M.D., F.A.C.P. Pp. 208; 43 illustrations. Springfield, Ill.: Charles C. Thomas, 1930. Price, $3.50.

THIS book deals with the epidemiologic and clinical aspects of tuberculosis in infancy, childhood and adolescence. The importance of contact with open tuberculosis, positive tuberculin reaction and roentgenologic examination in the diagnosis of pulmonary tuberculosis of the childhood type is emphasized as well as the relative unimportance of symptoms and physical signs. The author quotes liberally from current literature and summarizes our present knowledge of pulmonary tuberculosis in childhood. With the exception

of meningitis extrapulmonary tuberculosis is considered briefly. The usual difficulty is encountered that greatly reduced reproductions of roentgenograms intended to show caseous or calcified lesions of the lymph nodes in most instances do not illustrate. This book will not be of great value to the advanced student of tuberculosis but should prove instructive to physicians and public health workers who, without adequate knowledge of the disease, deal with large numbers of children. H. H.

MODERN OTOLOGY. By JOSEPH C. KEELER, M.D., F.A.C.S. Pp. 858; 105 illustrations. Philadelphia: F. A. Davis Company, 1930. Price, $10.00.

NOTHING new has occurred in otology in the past decade. On this account one is liable to view with tolerance the appearance of a new work on otology, as it so often is nothing more than another assembly of well-known facts written by someone who wishes to write a book. This work of the author, however, stands as a real contribution. The author has consulted a vast amount of literature, and the opinions on difficult subjects are not those of one, but of many observers. His chapters on embryology are especially good, and the presentation of clinical conditions is detailed and clear. A splendid bibliography is to be found at the end of each chapter. This book can certainly be recommended to the undergraduate, graduate student, general practitioner and specialist.

K. H.

HUMAN BIOLOGY AND RACIAL WELFARE. By Various Contributors. Edited by EDMUND V. COWDRY, PH.D. Pp. 612; 54 illustrations. New York: Paul B. Hoeber, Inc., 1930. Price, $6.00.

THIS book should be of interest to physicians and biologists as well as educated laymen. Twenty-eight distinguished scientists have set forth in nontechnical language the present knowledge in the several subjects that comprise the study of man. The reader is made to realize that each science depends upon the other, and that it is largely because of the progress in such fundamental disciplines as physics and chemistry that rapid advances have been made in general biology and in the biologic aspects of man. The first part of the book deals with the extent of life in time and space. There is a discussion of such interesting questions as "Are there other inhabited worlds than ours?" "How long has life existed in this world?" "How long may it continue to exist?" The second part deals with the origin of man and contains chapters on evolution and the human race. In the third part of the book there is a

discussion of man as a physiologic unit. The present Reviewer would particularly invite attention to the chapter by Professor Cannon on "The Integrative Action of the Vascular System." The fourth part deals with the effects of environment. Among the papers of special interest to physicians are those by Sir Humphry Rolleston on "What Medicine has Done and is Doing for the Race," and by Professor Zinsser in "Adjustment to Infectious Diseases." In the final part the future of mankind is discussed; there are chapters on the inheritance of disease, on population growth, the mingling of races, and on the shaping of human opinion.

B. L.

BOOKS RECEIVED.

NEW BOOKS.

The Surgical Clinics of North America, Vol. 10, No. 3 (New York Number, June 1930). P. 265; 123 illustrations. Philadelphia: W. B. Saunders Company, 1930.

The Medical Clinics of North America, Vol. 13, No. 6 (Mayo Clinic Number, May, 1930). Pp. 275; 55 illustrations. Philadelphia: W. B. Saunders Company, 1930.

Progressive Medicine, Vol. II, June, 1930. Edited by HOBART AMORY HARE, M.D., LL.D. Pp. 416; 51 illustrations. Philadelphia: Lea & Febiger, Inc., 1930.

Guy's Hospital Reports, Vol. 80, No. 2, April, 1930. By various contributors. Edited by ARTHUR F. HURST, M.D. Pp. 252; 14 illustrations. London: The Lancet, Ltd., 1930. Price, 12s 6d.

Collected Papers of the Mayo Clinic, Vol. XXI, 1929. Edited by MRS. M. H. MELLISH, RICHARD M. HEWITT, B.A., M.A., M.D., and MILDRED A. FELKER, B.S. Pp. 1197; 279 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $13.00.

*Surgical Diagnosis, Vol. III.** By 42 American authors. Edited by EVARTS A. GRAHAM, A.B., M.D. Pp. 1044; 446 illustrations. Philadelphia: W. B. Saunders Company, 1930. Price, $35.00, set of three.

*Alimentary Anaphylaxis.** By GUY LAROCHE, CHARLES RICHET FILS and FRANCOIS SAINT-GIRONS. Pp. 139. Berkeley: University of California, 1930. Price, $2.00.

*Allergie des Lebensalters.** By DR. CLEMENS PIRQUET. Pp. 170; 142 illustrations. Leipzig: Georg Thieme, 1930. Price, M. 23.

Anatomische Organkrankheiten aus seelichen Ursachen. By LEOPOLD ALKAN, M.D. Pp. 142. Stuttgart: Hippokrates-Verlag, 1930.

The Basis of Epilepsy. By EDWARD A. TRACY, M.D. Pp. 92; 17 illustrations. Boston: Richard G. Badger, 1930. Price, $2.00.

Infant Nutrition. By WILLIAMS MCKIM MARRIOTT, B.S., M.D. Pp. 375; 53 illustrations. St. Louis: The C. V. Mosby Company, 1930. Price, $5.50.

* Reviews of titles followed by an asterisk will appear in a later number.

Some Social Aspects of Mental Hygiene. By FRANKWOOD E. WILLIAMS, M.D. Pp. 214. Philadelphia: The American Academy of Political and Social Science, 1930. Price, $1.00 paper, $1.25 cloth.

Reprints of 21 papers on various aspects of this important question.

Chemical Methods in Clinical Medicine. By G. A. HARRISON, B.A., M.D., B.CH. (CANTAB.), M.R.C.S. (ENG.), L.R.C.P. (LOND.). Pp. 534; 65 illustrations. New York: The Macmillan Company, 1930. Price, $5.25.

*An Introduction to Vertebrate Embryology.** By H. L. WIEMAN. Pp. 411; 150 illustrations. New York: McGraw-Hill Book Company, Inc., 1930. Price, $4.00.

NEW EDITIONS.

Clinical Examination of the Nervous System. By G. H. MONRAD-KROHN, M.D., F.R.C.P. Pp. 222; 57 illustrations. Fifth edition. New York: Paul B. Hoeber, Inc., 1930. Price, $2.50.

This deservedly popular volume contains as added matter: Two illustrations—Diagram of the Action of the Different External Eye Muscles and Lipiodol Shadow in the Cul-de-sac under Normal Conditions, a few additional notes on Trophic and Vasomotor States, together with the recent, important work pertaining to Ventriculography and Encephalography.

Ultra-violet Rays. By PERCY HALL, M.R.C.S. (ENG.), L.R.C.P. (LOND.). Pp. 248; 64 illustrations. Fourth edition. St. Louis: The C. V. Mosby Company, 1930. Price, $4.50.

Four editions in six years testify to the demand for this kind of book.

Physiology and Biochemistry in Modern Medicine. By J. J. R. MACLEOD, M.B., LL.D., D.Sc., F.R.S. Pp. 1074; 295 illustrations. Sixth edition. St. Louis: The C. V. Mosby Company, 1930. Price, $11.00.

"Steady increase in general knowledge, rather than discovery, has been the feature of the advances in physiology during the past three years, so that the changes in the present edition are spread throughout the volume." For reviews of previous editions of this work see this Journal 1927, *173*, 723; 1923, *165*, 136 and 1919, *158*, 115.

Obstetrics for Nurses. By CHARLES B. REED, M.D., F.A.C.S., and CHARLOTTE L., GREGORY, R.N., B.S., M.D. Pp. 399; 144 illustrations. Third edition. St. Louis: C. V. Mosby Company, 1930. Price, $3.00.

Minor Surgery. By ARTHUR E. HERTZLER, M.D., and VICTOR E. CHESKY, M.D. Pp. 602; 475 illustrations. Second edition. St. Louis: C. V. Mosby Company, 1930. Price, $10.00.

The second edition of this book presents few changes from that of the first. Some 37 illustrations have been added and such additions to minor surgical procedures are given as a paragraph on injection treatment of varicose veins, and so forth. The book remains a very good and well illustrated minor surgery including, however, the technique of operations of many surgical procedures which could hardly fall into the minor surgical group.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

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AND

JOHN H. MUSSER, M.D.,

PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

Streptococci from Scarlet Fever, Erysipelas and Septic Sore Throat.—There has been a feeling among many bacteriologists, immunologists and even clinicians that the microörganisms responsible for scarlet fever, erysipelas and septic sore throat are very closely related, so closely, as a matter of fact, that it has been demonstrated more than once that the streptococci from septic sore throat and these other two diseases cannot be separated by toxin production and agglutination and that the toxins from streptococci from septic sore throat are rendered nontoxic by scarlet-fever antitoxin. TUNNICLIFF (*J. Am. Med. Assn.*, 1930, **94**, 1213) has studied colonies of human streptococci on chocolate agar, a culture medium which contains defibrinated sheep's blood, Liebig's beef extract and agar. Using this particular medium in the study of the streptococci of the three diseases mentioned above, she finds that on the chocolate agar the color reaction differs, when streptococci are isolated from cases of scarlet fever, from those isolated from patients suffering from erysipelas. She believes that this is further evidence of their etiologic difference. The author mentions, also, that she has examined by the opsonic method strains of streptococci isolated during epidemics of sore throat. It is found that they belong neither to the scarlet fever or the erysipelas group. The strains from septic sore throat were capable of producing a bright green color on chocolate agar and the cultures from the two types of streptococci produced colonies which are quite distinct. One is warranted in feeling that as a result of these studies there is an etiologic difference between the three groups of streptococci. The reader would be definitely convinced were there not other observations so totally divergent in their results.

Relation of Diet to the Production of Dental Caries in Young Rats.—One of the statements frequently made by dentists is that dental caries occurs in children as a result of vitamin deficiencies. Furthermore, the statement is often made that it may be produced likewise by a deficiency of mineral salts. KNOWLTON (*Proc. Soc. Exper. Biol. and Med.*, 1930, **27**, 757) selected a variety of diets which were fed to rats from an inbred colony. Thirty-seven rats were kept on these varied diets, usually for an average of about forty-five days. The biologic incompleteness of the diet is indicated by the marked reduction in growth of the test animals as contrasted with the controls. There was a significant difference also in the calcium and phosphorus content of the teeth of the rats which were on one of the test diets. The young rats in no case developed dental caries. "The tests indicate," says the author, "that in the young rat dental caries probably does not result from the use of diets low in vitamin A, B or D or by a deficiency of mineral salts."

Neutralization of the Virus of Poliomyelitis by Human Sera.—SHAUGHNESSY, HARMON and GORDON (*Proc. Soc. Exper. Biol. and Med.* 1930, **27**, 742) review somewhat briefly the literature on the neutralization of the virus of poliomyelitis by the sera of individuals recovered from an attack of the disease. The reactions, however, have never been studied in a quantitative manner. In the present experiments, Berkefeld filtrates of 5 per cent emulsion of spinal cord containing the virus were mixed in 1.5 cc. quantities with an equal quantity of the serum dilution studied, incubated at 37° C. for two hours and 2 cc. injected into the brain of the monkey. Their results are presented in tabular form; suffice it here to say that the sera of contacts, of normal adults and of children have an equal power at least, and probably more power, to neutralize the virus than the sera of people who have had the disease. The sera of infants seem to be almost lacking in effect upon the virus. The important feature of the study, of course, is that normal sera may be used in the therapeusis of poliomyelitis.

Effect of Bile Salts on the Blood Calcium.—In jaundice it has been known for some time that there is disturbance of calcium metabolism and recently the disorder has been treated in a certain number of instances by the intravenous injection of calcium chlorid. This has usually been the method employed in order to increase blood coagulation time preparatory to surgical operation, but at the same time it has been noted that there has been a considerable improvement in the symptom of jaundice. The blood calcium has been shown to be extremely low in this condition. EMUND ANDREWS, REWBRIDGE and HRDINA (*Proc. Soc. Exper. Biol. and Med.*, 1930, **27**, 755) undertook to investigate certain phases of disturbed calcium metabolism in jaundice. They injected a 10 per cent solution of bile salts intraperitoneally into dogs and administered it likewise to another group intravenously and very promptly there occurred marked lowering of this blood calcium. Following a short preliminary rise there was this marked fall. The authors are not prepared to give an explanation of this phenomenon, but point out that the obvious fact of the insolubility of the calcium compounds of bile acids suggests their precipitation.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

Papillomas of Choroid Plexus.—VAN WAGENEN (*Arch. Surg.*, 1930, **20**, 199) says that two cases of papilloma of the choroid plexus are reported. In one the tumor was surgically removed from the left lateral ventricle, with relief of symptoms. The second case represents the observation at necropsy of a huge papilloma of the choroid plexus with true "seeding" of the tumor *via* the cerebrospinal fluid. The reports of about 45 cases have been collected from the literature which, so far as one can determine from the descriptions given, seem to have arisen from the choroid plexus. A few of these presented the phenomenon of seeding. The favorite site for these tumors is in the fourth ventricle. The age incidence was greatest in first decade and gradually diminished up to the sixth decade. The surgical removal of this type of tumor is feasible, especially with the aid of electrosurgical devices. Preliminary Roentgen treatment in the author's cases appeared to have reduced the vascularity greatly. A considerable part of the nonobstructive hydrocephalus found with tumors of the choroid plexus may well be associated with the increased epithelial surface.

Chronic Recurring Temporomaxillary Subluxation.—MORRIS (*Surg., Gynec. and Obst.*, 1930, **50**, 483) writes that temporomaxillary subluxation is a definitely distinct entity, the pathologic condition of which is characterized by a distortion of the normal relations of the joint meniscus leading to capsular relaxation. Resulting disturbances in joint mechanics are responsible for a variety of joint dysfunction best known as snapping jaw. Commonly seen as a painless, noisily functioning joint the efficiency of which is not at all impaired, it is occasionally encountered in the form of chronically recurring attacks of pain and locking, requiring immediate treatment. There exists an unexplained reluctance to apply to this joint the radical operative measures, which have become the accepted treatment for analogous minor lesions of other joints. Failure to take into consideration the pathologic physiology of temporomaxillary subluxation has been responsible for a large number of proposed methods of treatment representing a wide divergence of principles. Two methods of treatment are emphasized which are based upon sound surgical principles and upon a study of the mechanics of the joint. Utilization of these methods should standardize treatment and demonstrate the practicability of accepting a larger group of these cases for radical operation.

The Indwelling Ureteral Catheters in Urinary Surgery.—GUTIERREZ (*Surg., Gynec. and Obst.*, 1930, **50**, 441) states that the indwelling ureteral catheter is of value in urinary surgery, not only in regard to diagnosis and treatment but as a convenience during and after opera-

tion. It is essential that the catheter must serve its purpose, that is, secure drainage, relieve pain and correct infection. When double drainage is required the special urethral catheter should be easily passed, it being inserted through the inlying ureteral catheter. The most striking results are obtained with this method of treatment in "renal colic," ureteral calculi, pyelitis and pyelonephritis, the so-called idiopathic hematuria, urinary stasis with or without infection and in calculous anuria. Also in certain instances when elimination of urine is insufficient, forced fluid and daily intravenous infusion are highly desirable. After operation it will serve to secure drainage and prompt healing of the wound without leakage of urine or the formation of permanent fistula. Also after operation it will serve too to divert the urine from the bladder, particularly in operations on vesicovaginal fistulæ, thus permitting the bladder to heal without infection from urine. The technique of the indwelling ureteral catheter is merely that of cystoscopy and catheterization of the ureters.

Phrenic Exairesis in the Treatment of Pulmonary Tuberculosis.—FRANK and MILLER (*Ann. Surg.*, 1930, **91**, 669) believe that phrenicectomy is a valuable aid in the treatment of pulmonary tuberculosis in selected cases. Of 100 patients so treated, 90 per cent of whom were far advanced, 40 per cent showed improvement. In 8 the sputum became negative for tubercle bacilli and in 8 the cavities disappeared. Phrenicectomy is an adjuvant in artificial pneumothorax, and should be considered in every case with cavitation. Following avulsion of the phrenic nerve 44 per cent of the cases showed a better collapse. A good phrenicectomy is better than a poor pneumothorax. It is less hazardous, less discomforting, unattended with complications and is a necessary preliminary to thoracoplasty. The good results of phrenicectomy are not dependent on the location of the pathology, but rather on the retractibility of the pulmonary tissue. Basal and midlobe lesions offer most and cavities above the clavicle least, although in the latter with a marked elevation of the diaphragm good results are obtained.

Treatment of Bronchiectasis: Multiple Stage Lobectomy.—CORYLLOS (*Arch. Surg.*, 1930, **20**, 767) says that a clinical classification distinguishing different forms of bronchiectasis is suggested, and the practical usefulness of these distinctions has been set forth. The necessity for using a prolonged and progressive treatment against a chronic and progressive disease is shown. In advanced forms of bronchiectasis only eradication of the diseased parenchyma of the lung can produce a cure. This, according to the case, should be done by resection (lobectomy), cauterization, cautery pneumectomy of Graham or exteriorization (Whittemore). In order to decrease the mortality incident to these operative procedures, a technique of multiple stage lobectomy is outlined in which the following stages are systematically performed in the order named: Artificial pneumothorax, phrenicectomy, thoracoplasty and lobectomy. In support of this method, physiologic, pathologic and clinical data have been presented. Two cases of advanced bronchiectasis, in which cure was achieved by the use of this technique, are reported.

THERAPEUTICS

UNDER THE CHARGE OF

CARY EGGLESTON, M.D.,

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AND

SOMA WEISS, M.D.,

ASSISTANT PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

Comparative Studies of a Heart Hormone Preparation and Extract of Voluntary Muscle.—FAHRENKAMP and SCHNEIDER (*Med. Klin.*, 1930, **26**, 48) report the results of comparative studies on man of an extract of heart muscle previously believed by Haberlandt to represent a cardiac hormone and an extract of voluntary muscle prepared so as to be free from albumin, histamin and epinephrin. They find that the extract of voluntary muscle produces identically the same effects as does that obtained from the heart muscle and they therefore conclude that there is no evidence in favor of the latter representing a true heart hormone. The actions manifested by these two extracts are marked slowing of the ventricular rate, both in fibrillating patients and in those with sinus rhythm when the extract is administered to patients orally under the influence of digitalis. Both extracts administered either orally or intravenously to patients with recurring seizures of angina pectoris control the attacks almost completely. However, if administered to patients under the influence of digitalis, the extracts may produce symptoms of angina pectoris. In patients with continued very high blood-pressure and sleeplessness the continued use of these extracts improves the patient's subjective symptoms and usually leads to a return of the ability to sleep. For oral use a dose of from 15 to 60 drops per day usually suffices. In severe cases of angina, more immediate action is obtained by an intravenous dose of from 1 to 2 cc. At present the dosage must be regarded as experimental. Intravenous administration of a dose of 1 cc. produces a transitory sense of warmth in the head accompanied by redness of the face, both of which phenomena disappear within two or three minutes. Occasionally the patient complains of a pulsating, painful sensation in the upper abdomen. This also is harmless and passes rapidly. Patients with high blood pressure usually show a fall of from 10 to 30 mm. of mercury, while those without high blood pressure frequently show a transitory rise of about the same amount.

The Action of Some of the Newer Drugs on the Circulation.—Finding that there is an inadequacy of trustworthy information with reference to the actions of a number of the newer remedies in states of circulatory insufficiency, TRENDELENBURG (*Med. Klin.*, 1929, **25**, 1573) reports the results of a careful analysis of several of these drugs on the basis of his own pharmacologic experiments. He concludes that, for the relief

of true cardiac insufficiency, digitalis and strophanthus are unrivaled. They have the great advantage over all other drugs advocated for use under these circumstances of improving the work of the heart without exercising any significant constrictor effect upon the peripheral blood-vessels and, therefore, without increasing the peripheral load against which the heart must work. Both epinephrin and ephedrin stimulate the heart powerfully but simultaneously constrict the peripheral arteries so that their stimulant effects upon the heart are largely overcome by the increased peripheral resistance. Cardiazol, coramin and hexeton have exceedingly little or even no action upon the circulation which will overcome cardiac failure and hence are practically useless in that condition. They, however, do produce a transitory stimulation of the depressed respiratory center and may be of slight benefit thereby in diminishing the lack of oxygenation of the blood and in increasing elimination of carbon dioxid. In the very rare condition of true vascular insufficiency epinephrin and ephedrin are far the most useful drugs. Digitalis and strophanthus are of no value and cardiazol, coramin and hexeton are too feeble in their effects upon the vasomotor mechanism to be trustworthy. Where there is a combination of cardiac insufficiency with vascular insufficiency, epinephrin and ephedrin again are the drugs of first choice while the other two discussed here are of relatively little value. They must be employed however with great care in order to avoid overconstriction of the bloodvessels and thereby do greater harm than good. Cardiazol, coramin and hexeton may sometimes be somewhat helpful in combination with either digitalis or epinephrin where there is a considerable degree of respiratory depression, but alone none of these agents is capable of overcoming either of the two forms of circulatory deficiency.

Investigations on the Peroral Insulin of Stephan (Cholosulin).—STEPHAN (*Deutsch. med. Wchnschr.*, 1930, **56**, 88) reports further studies on the action of his peroral form of insulin. This preparation is an addition compound of insulin with the sodium salt of desoxycholic acid. He contends that, when properly administered, that is when given to the patient during fasting, this preparation permits the absorption of insulin through the portal vein. Only a portion, however, of the insulin so administered and absorbed exerts an immediate action, the remainder according to his contention being fixed in the liver and giving rise to a prolonged and evenly-sustained insulin action. Investigations confined to a period of a few hours, therefore, seem to show that this preparation is much less active in the control of diabetes than is the usual preparation of insulin administered subcutaneously. In order to test the theory that this partial fixation of insulin is due to absorption through the portal vein, Stephan reports investigations embracing the use of his preparation by subcutaneous injection both in normal individuals and in diabetic persons. From these investigations he finds a similar mild early insulin action both on blood sugar and on glycosuria and a prolonged late action due to temporary fixation. He concludes that the combination of insulin with desoxycholic acid is responsible for this altered action. He also contends that the use of

cholosulin is never accompanied with the danger of insulin shock in either normal or diabetic persons and that even with very large doses its optimal action is not exceeded owing to fixation of a large portion of the dose. The preparation thus differs essentially from ordinary insulin, bringing about a mild initial action which is followed by a well-sustained control of blood sugar. However, Stephan does not believe that the preparation is inferior to ordinary insulin in the control of diabetes, whether it be given by mouth or by subcutaneous injection.

UMBER and ROSENBERG (*Deutsch. med. Wchnschr.*, 1930, **56**, 169, 213) subjected Stephan's cholosulin to a very accurately controlled investigation in a small group of cases, administering it exactly as recommended by Stephan both by mouth and by subcutaneous injection. They find that only with exceedingly large doses, 100 to 500 units, is there even a mild diminution of glycosuria. In the most favorable instances in man, only 5 per cent of the insulin so administered by mouth becomes active in the burning of sugar. The antiglycosuric action of cholosulin is so small and so uncertain that the preparation cannot be considered of value in the treatment of diabetes when administered by mouth. The authors are able to find no qualitative differences between the action of cholosulin and ordinary insulin and are unable to discover any evidences of its temporary storage and subsequent release in the body. The action of cholosulin administered by mouth is so uncertain and so insignificant that the authors find no definite evidences of its capacity to diminish alimentary glycosuria. They find essentially the same deficiencies when this preparation is administered subcutaneously, although under these circumstances there is a slightly delayed reduction in the blood sugar appearing from six to nine hours after injection. However, in controlled experiments, a delayed fall in blood sugar of equal magnitude is observed after the injection of 1 gm. of desoxycholic acid and an equal fall occurs even in well-controlled cases to whom no medication is administered. From their investigation the authors conclude that there is no evidence that Stephan's cholosulin is of any practical value in the treatment of diabetes.

PEDIATRICS

UNDER THE CHARGE OF

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Underweight Children—Increased Growth Secured Through the Use of Wheat Germ.—MORGAN and BARRY (*Am. J. Dis. Child.*, 1930, **39**, 935) compared two groups including from 31 to 47 underweight children between the ages of eleven and thirteen years as to growth in weight, height and certain other physical measurements over three periods

totaling thirty weeks. Each child in one of these groups in each period was required to include in the noon meal 3 ounces of rolls made with 50 per cent wheat germ and 50 per cent white flour. A control group took the usual white flour rolls. The test group took a total of 5 ounces of wheat germ per week. It was noted that the weight increases in each of the wheat germ periods were about three times as great as in the control periods. The difference in all cases was five or more times greater than the probable error of the difference. The height increases were significantly greater in two of the wheat germ periods than the two of the corresponding control groups. Alveolar carbon dioxid tension was increased in a greater percentage of the wheat germ-fed children than in the controls and it is thought that this change was due to the diminished acidosis following increased food intake. The significance of these observations is based on the recent discovery of the multiple nature of vitamin B and of the poverty of the major foods such as fruits, vegetables, milk and meat in the antineuritic substances. The authors point out the importance of whole cereals but most particularly of grain embryo such as those of wheat and rice as a possible source of this vitamin. They also point out probable relationship of the decreasing vitamin B content of the modern diet to decreased appetite in children, nervousness, constipation and possibly other gastrointestinal disturbances.

Chronic Subdural Hematoma in Infants.—Sherwood (*Am. J. Dis. Child.*, 1930, **39**, 980) presents 9 cases in which he describes a definite clinical syndrome. The pathologic changes in the disease called pachymeningitis interna hemorrhagica may vary considerably due to the fact that in the past many conditions involving the dura have been described as pachymeningitis. The term chronic subdural hematoma describes the condition found in the 9 cases presented in his report. The etiology is obscure and it was unusual to find that in 5 of the 9 cases the patients were cared for in institutions or by foster-mothers. Trauma due to injury at birth or other means is a possible factor although in these particular cases it was not proved. Infection is important only as a complication. Syphilis is also a possible cause as is also a bleeding diathesis but the latter could not be proved in any of these cases. This condition should be thought of in every case in which there are convulsions and enlargement of the head and should be confirmed by a subdural tap. This operation should be done with a hypodermic needle with a small syringe in order to avoid trauma to cerebral veins in case no chronic subdural hematoma is present. After the diagnosis is established a small lumbar puncture needle can be used to drain the cyst under the strictest asepsis as these hematoma easily become infected. After the active process has subsided the patient should have the benefit of a neurosurgical consultation in order that more definite treatment can be used, if necessary. The prognosis as a whole is good in the absence of intercurrent infection, but everything should be done to raise the patient's general resistance in order to prevent such an occurrence. Many cases are followed by a sequela.

The Use of Gelatin as a Supplementary Food in the Infant's Dietary.—Elterich, Boyd and Neff (*Arch. Pediat.*, 1930, **47**, 286) studied 11 cases of whom 7 were males and 4 were females. Of this group there were 5 colored and 6 whites of whom one was Italian and one was Russian. These infants were studied on 1313 experimental days of which 719 were gelatin days and 594 were not gelatin days. There was a gain per twenty-four hours on gelatin of 0.85 ounces. There was gained per twenty-four hours not on gelatin 0.98 ounces. The average gain per twenty-four hours was 0.91 ounces. These results show that babies average about 1 ounce less in gain per week when on gelatin although the same number of calories were used. These results are according to expectations for when gelatin was given the formula contained a very high protein content, while when gelatin was not used the formula contained an average of protein and carbohydrate. It is a well-known fact that babies frequently gain rapidly on the excessively high-carbohydrate diet as is seen in babies fed on condensed milk, for this reason the increase in weight should not be the only standard used in the estimation of the healthy growth of infants. Such points as tissue turgor and hard, well-developed muscles are important considerations. It was noted by the observers that many factors which have been discussed by others such as tracheal coughs, running nose, and other parental infections almost invariably influenced the gain in weight. In spite of the relative large amount of protein in these gelatin formulæ no evidence of the so-called protein fever was observed. This absence of protein fever may have been due to the ample supply of liquid in the diet, a fact that was originally pointed out by Finkelstein. During certain periods of the observation, three times the quantity of protein matter was given to the infants that is given in the average every-day formulæ. This high-protein feeding was maintained for stretches of more than three weeks without any apparent untoward results.

Nephritis in Childhood.—Aldrich (*J. Am. Med. Assn.*, 1930, **94**, 1637) has been accustomed not to limit the fluids in any case of nephritis regardless of the amount of edema present. He follows this method of treatment because he felt that patients were toxic and that withholding of liquids could not be sound therapeutics in some patients. He suggests that edema may be a protective mechanism designed to dilute toxins. He feels that this method of treatment is justified by the observations that he has made that patients are much less toxic and more comfortable during the administration of sufficient fluids and he does not fear edema except in those cases where it involves the brain, lungs or larynx. On the other hand he has found that definite restriction of liquids has been responsible for accidents which have occurred in his experience. As a result of his feeling toward fluid he has evolved a technique for the treatment of convulsive anemia which has been used with great success in the elimination of accidents from this cause.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Arsenic Findings in Eczema and Allied Conditions in Infants and Young Children.—Van Dyck, Throne and Myers (*Arch. Pediat.*, 1930, **47**, 218) carried on the previous work of Throne and Myers in a study of the possibility of arsenic as an etiologic factor in eczemas. Urine specimens from 105 infants and young children with eczema or urticaria were examined for arsenic, using Myers' modification of the Marsh test. In 50 cases (48 per cent) no arsenic was found; the remaining 55 cases showed the presence of arsenic ranging from 0.04 to 2.3 mg. per 100 gm. of the dried specimen. Eleven control patients with one exception gave negative results. The single instance was the discovery of 0.12 mg. of arsenic in a young child who had previously received thallium acetate for tinea capitis. The controls represented such conditions as impetigo, scabies, acute dermatitis and pediculosis. Breast-milk specimens from mothers who were nursing babies with eczema contained arsenic in 40 out of 55 cases examined (72 per cent). The amounts ranged from 0.012 to 3.5 mg. per 100 gm. of solids. Fifteen normal controls were negative for arsenic except 2 specimens which contained 0.06 and 0.09 mg. The sources of arsenic are widespread and are found in all sorts of foods, including fruit, vegetables, fish, milk and candy. Sodium thiosulphate in salol-coated tablets, of 2½ grains each, and given three times a day before meals, seemed to be almost specific in cases where large amounts of arsenic were found. For infants the tablets were crushed and the powder given with the milk or cereal. In some cases where no arsenic was found the sodium thiosulphate seemed to give temporary relief. The authors' work, in their opinion, justifies the previous conclusions of Throne and Myers, that arsenic is an important factor in about 30 per cent of cases diagnosed clinically as eczema.

A List of Cutaneous Irritants.—Under this title Weber (*Arch. Dermat. and Syph.*, 1930, **21**, 761) has listed a complete outline of all known and reported cutaneous irritants that have been productive of dermatitis and eczema. The irritants are classified under Hair Dyes and Hair Tonics, Cosmetics, Irritating Plants of the United States, Tropical Plants and Unclassified Irritants in Alphabetical order. The inclusion of a comprehensive bibliography makes this a most usable contribution. The American Medical Association is publishing this report as part of its series of pamphlets for ready reference.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Surgical Treatment of Cancer of the Cervix.—Due to the fact that radium is so extensively used in this country in the treatment of cancer of the cervix, it has been necessary for some years to turn to European clinics in order to determine the present status of the radical operation. BONNEY (*Lancet*, 1930, **218**, 277), who is one of the foremost English gynecologists, states that he has performed 382 Wertheim operations, of which 284 were done over five years ago and, therefore, are of value in determining the end results. His analysis of this series is as follows:

Immediate mortality	47	(16.5 per cent)
Recurrence within five years	107	
Untraced	12	
Died of intercurrent disease	8	
Well at the end of five years	110	
	284	

He is convinced that the mortality of the operation decreases with increasing experience of the operator, and as evidence presents the following table:

	Operations.	Deaths.	Mortality, per cent.
1907 to 1910	110	22	20.0
1916 to 1924	174	25	14.3
1925 to 1929	98	8	8.1

The factors which have been of value in the reduction of the mortality include spinal anesthesia in combination with full ether anesthesia in order to combat shock; packing the vagina tightly with gauze soaked in violet green to combat infection; protection of the abdominal wound with two layers of rubber dam and the use of automatic retraction; separation of the bladder and rectum from the vagina by the sense of touch; exposure of the uterine arteries before ligation close to the internal iliac arteries; complete isolation of the lower 2 inches of the ureters; division of the cardinal ligaments by the sense of touch; extensive removal of the vagina, the lower end which remains being left open and the extirpation cavity in the pelvis packed so that the packing comes out at the vulva; and finally, the routine removal of the regional glands. While he has performed the operation in as short a time as twenty-seven minutes, he has found that his average time is about one

and a quarter hours. Immediately after operation he gives intravenous saline solution or blood transfusion in order to anticipate shock. He does not see any advantage in using radiation as an adjunct to operation either pre- or postoperatively. Of the 284 cases in this series, the regional glands removed were cancerous in 124 and not cancerous in 160, so that the gland involvement rate was 43 per cent. The five-year survival rate for the gland-free group was 49.9 per cent as compared with 23.3 per cent for the gland-involved group. Of his private cases, on which he has very careful records, his operability rate in 106 cases seen was 78 per cent, with relative cure in 48 per cent and absolute cure in 37.5 per cent. Of this group there was gland involvement in 40 per cent of the cases operated upon. In view of such excellent results, naturally he is very enthusiastic about operation, believing that the best results in the treatment of cancer of the cervix are to be obtained by operation by skilled surgeons in all operable cases, while the remainder should be treated with radium. We are not at all surprised at Bonney's views on this subject when backed by statistics which are so good, but there are few clinics, let alone individual surgeons, where such results can be equalled or even approximated, and it is for this reason that the large majority of gynecologists have abandoned the radical operation in favor of irradiation.

Treatment of Complicated Dermoid Cysts.—In describing some of the complications to which ovarian dermoid cysts are subject and the appropriate treatment, COUNSELLER (*Surg. Clin. North America*, February, 1930, p. 151) states that the diagnosis of dermoid cyst is rarely made before operation, as they are comparatively slowly growing tumors. They often become fixed in the pelvis by attachment to the rectum or vagina and then become secondarily infected. When suppuration occurs perforation into the rectum, vagina or bladder usually takes place, and the resultant fistula is apt to remain for months or years unless the content of the cyst is completely evacuated. In such cases it is far safer to dilate the fistulous tract, evacuate the cyst as thoroughly as possible and scrape the inner wall with a sharp curette so as to eradicate the epithelial lining and all dermoid structures. If the wall of the cyst has not been punctured by the curette the cavity should be irrigated thoroughly with warm salt solution and packed solidly with iodoform gauze. The gauze is gradually removed and the cyst and fistulous tract will contract down to a scar. He cautions that it is extremely difficult and dangerous to remove a dermoid cyst which has perforated externally by the abdominal route on account of the high risk of general peritonitis, the deep situation of the tumor in the pelvis and the dense adhesions of the wall of the cyst to adjacent structures. In cases in which torsion of the pedicle of a cyst has been diagnosed, abdominal exploration should be immediately performed. As a rule, in such cases the blood supply is practically shut off and if the cyst is a dermoid it may perforate into the peritoneal cavity and produce fatal peritonitis.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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Permanent Relief of Pain in Absolute Glaucoma and Ciliary Neuralgia by Anesthetization of the Gasserian Ganglion.—Two problems are still unsolved in the treatment of pain in ophthalmology: permanent relief of pain in the blind eye, which should be retained for cosmetic reasons, and the permanent relief of pain in the functioning eye. Resection of the ciliary ganglion frequently leads to permanent paralysis of ocular muscles, to perforation of the sclera necessitating later enucleation. Orbital injection of alcohol also may be followed by paralysis of the ocular muscles and its success and permanence is uncertain. To avoid all these undesirable sequelæ ALEXANDER (*Klin. Monatsbl. f. Augenh.*, 1930, **84**, 65) recommends alcohol injection of the Gasserian ganglion such as is done in trigeminal neuralgia. He reports 2 successful cases: in the first there was pain in the right eye and entire side of the head due to secondary glaucoma following thrombosis of the central retinal vein. Continuous vomiting accompanied the pain. Alcohol injection resulted in permanent anesthetization of the first and second branches and absence of corneal reflexes. Full sensibility was retained in the third branch. The vomiting ceased as soon as the pain was relieved. There has been permanent relief for two years. In the second case uncontrollable pain was present in the first branch, particularly in the eye which was functioning. The first injection of alcohol gave relief for a year; the second injection was given as soon as there was a slight recurrence. The permanent relief has lasted more than five years. There is full visual acuity and a smooth cornea; the corneal reflex is absent. Alexander considers that alcohol injection of the Gasserian ganglion is the only method which will give permanent relief without cosmetic deformity in uncontrolable pain in the blind and particularly in the functioning eye.

Alcohol Injections in the Treatment of Blepharospasm and of Spastic Entropion.—Essential blepharospasm is much more difficult to treat than symptomatic blepharospasm in which the basic disease may be attacked and the spasm relieved. Alcohol injections to produce akinesia of the facialis without paralyzing it has been used by SAFAR (*Ztschr. f. Augenh.*, 1930, **71**, 135) and others with success. The author injected about 2 to 3 cc. of 4 per cent solution of novocain followed by 2 to 3 cc. of 80 per cent alcohol to obtain the greatest possible blocking of the afferent fibers of the facialis. The novocain mitigates the burning sensation caused by the alcohol. The injection is made uniformly, corresponding to the temporal circumference of the orbital border outside the orbital border; the depot is placed into the muscle, not subcutaneously. The action of the injection is immediate. The author reports 2 cases of blepharospasm in which he has used this akinesia

and 2 in which he has used it in spastic entropion. In these 2 instances he used only "half akinesia"—1 to 1½ cc. alcohol. He recommends the treatment because it is slight and ambulatory and warrants further use.

Metastatic Bacillus Coli Panophthalmitis from Calculus Pyonephrosis.—While metastatic panophthalmitis is not uncommon, Bacillus coli infection in such cases is rare and no case of proven infection from the kidneys has been reported. Experimental work has shown that bacteria can pass from the blood stream into the vitreous of normal, unirritated eyes. Injured eyes are more favorable for their entrance. There are three types of inflammation: An intense one, with symptoms of panophthalmitis and possible rupture; iridocyclitis, with hypopyon, vitreous complications and eventual atrophy; an insidious, slightly inflammatory condition which gradually becomes apparent and in children simulated glioma. LEVINE (*Arch. Ophthalmol.*, 1930, **3**, 410) reports the case of a man, aged thirty-eight years, in whom the metastatic infection could be traced to the kidneys. The patient came complaining of redness and pain in the eye. Two days previous he had had a left-sided renal colic; he had had similar attacks for six years. The right kidney had been removed seven years ago for calculus pyonephrosis. The inflammation of the eye increased, so that two days later an incision was made to allow the escape of pus which was cultured and then evisceration was performed. The culture proved to be a pure growth of Bacillus coli. A similar pure growth was obtained from a catheterized specimen.

Argyll-Robertson Pupils in Polyneuritis: Report of a Case and Theoretical Deductions.—In all, NIELSEN and VERITY (*Ann. Int. Med.*, 1930, **3**, 707) have listed fifteen causes of Argyll-Robertson pupil: Syphilitic processes; disseminated sclerosis; polioencephalitis; diabetes mellitus; sulphid poisoning; congenital; syringobulbia; diffuse toxi-infective states; finally, a case in which no cause could be found, but which progressed through the Argyll-Robertson to complete ophthalmoplegia interna, but with development of pupillary contraction whenever the patient swallowed anything. The authors now present another case in which Argyll-Robertson pupil appeared in polyneuritis; it seemed to them to bear out Ingvar's theory as to the pathology of reflex immobility. Ingvar considers that only such processes as manifest themselves in producing marginal destructions within the basal subarachnoid spaces of the brain are able to cause the Argyll-Robertson pupil. The patient, a man, aged sixty-two years, was admitted to the hospital with acute polyneuritis apparently of a toxic and not syphilitic nature. Argyll-Robertson pupil was found which had completely disappeared at the end of nine days. With the regression of the polyneuritis the optic neuritis also diminished. Evidence of central neuritis could not be shown above the level of the D8 segment; bilateral optic neuritis and considerably increased globulin in the spinal fluid was found. There was, therefore, inflammation of the regions traversed by the afferent pupilomotor fibers. With the onset of this inflammation Argyll-Robertson pupil appeared and with its regression disappeared. The authors, therefore, consider that this case corroborates Ingvar's explanation of the pathogenesis of reflex immobility of the pupils.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Osteogenesis of the Human Periotic Capsule.—The petrous portion of the temporal bone and especially the otic capsule is of interest from a purely embryologic and anatomic standpoint because of its unique structure. In the realization that a thorough knowledge of the development and structure of this bone may prove of importance in solving the mystery surrounding otosclerosis and its supposed relation to that dreaded disease—progressive deafness, BAST (*Arch. Otolaryngol.*, 1929, **10**, 459) calls attention to the fact that the texture of the bone in the otic capsule differs from that of the other bones and that the outstanding difference is the normal presence of so-called calcified cartilage. Inasmuch as the significance of this incomplete replacement of cartilage by bone in this particular bone and not in other bones is still unknown, the author, in full recognition of the importance for a better understanding of this structure, sets forth a detailed account of his observations concerning the osteogenesis of the bony otic capsule. Following a masterful presentation, supplemented by microphotographs, Bast concisely summarizes his findings. This recapitulation includes such pertinent anatomic data as : (1) the bone of the periotic capsule is of three types—perichondral, endochondral, and intrachondral; (2) an exposition by the process by which the ossification of the cartilaginous capsule begins; (3) a description of an area known as fissula ante fenestram (Siebenmann) or Cozzolino's zone (Perozzi), and (4) of another structure known as canalis membranceus cæcus (Ibsen) or as fossula post fenestram (Siebenmann).

Otosclerosis in Its Histogenic Relations to Osteodystrophia Fibrosa (Ostitis Fibrosa).—Having established a foundation for further studies of bone pathology—especially osteodystrophia fibrosa and otosclerosis—in a previous communication,[1] and inasmuch as no special critical comparison of these two diseases from the standpoint of histogenesis has appeared considering the most recent contributions to the pathology of osteodystrophia fibrosa, WEBER (*Arch. Otolaryngol.*, 1930, **11**, 1) reports a very comprehensive study in this connection. In contradistinction to earlier authors, the question of otosclerosis is approached from studies made on osteodystrophia fibrosa, which is kept in the limelight. Weber regards the present contribution as supplementary to his recent publication having to do with the nature of osteodystrophia fibrosa (*Beitr. z. allg. Pathol. u. path. Anat.*, 1929, **82**, 383). Briefly, Weber has concluded from his observations that both otosclerosis and osteodystrophia fibrosa represent a degenerative, reactive, reparative process. The typical focal otosclerosis is histogenetically identical

[1] *Vide* retrospect: AM. J. MED. SCI., 1929, **178**, 292.

with a local osteodystrophia fibrosa and may be regarded as a local hyperostotic porotic or local hyperostotic sclerotic form of osteodystrophia fibrosa, an "osteodystrophia otosclerotica." It belongs to the metapoietic diseases. Only the cases representing such focal involvement of the labyrinthine capsule ought to be designated as otosclerosis (genuine otosclerosis). In cases of generalized osteodystrophia fibrosa the diagnosis "otosclerosis" is possible, from the histopathologic standpoint, only in von Recklinghausen's disease (ostitis fibrosa) and then only in case the changes are superimposed and themselves represent as hamartoplasia the pseudotumor. The localization of the genuine otosclerosis in the majority of these cases leads to deafness due to stapedial ankylosis (so-called clinical otosclerosis). It is possible, however, that some of these cases with typical histopathologic otosclerosis do not reveal the clinical aspect of otosclerosis, namely, ankylosis of the stapes. Contrariwise, it is possible that certain cases with no histopathologic otosclerosis may reveal the clinical aspect of otosclerosis owing to stapedial ankylosis. These cases must be regarded not as otosclerosis, but rather as a purely generalized osteodystrophia fibrosa.

A Contribution to the Etiology of Progressive Deafness. Preliminary Report.—In a study of the acinous and insular function of the pancreas in 9 cases of otosclerosis and 12 cases of nerve deafness, GOTTLIEB (*Laryngoscope*, 1930, **40**, 85) found definite lowering of the digestive capacity in one or more of the pancreatic ferments in fourteen instances, and blood sugar levels higher than the average normal in five. Although the majority of cases treated with pancreatic extract showed improvement, the author is skeptical as to the conclusive value of this therapy in progressive deafness, especially in otosclerosis. Of the 4 patients with nerve deafness who were given pancreatic extract, all improved. The audition in 4 of the 5 persons yielding high blood-sugar values or glycosuria became more acute after treatment.

Studies in Action Currents in Laryngeal Nerves.—In order to ascertain more about the neurophysiologic mechanism of phonation, LINDEMANN (*Proc. Soc. Exper. Biol. and Med.*, 1930, **27**, 479) recorded action currents from the inferior and superior laryngeal nerves during voice production in dogs, using a 3-element Westinghouse oscillograph. It was found that when no voice was produced the action current line was practically at rest, whereas during voice production the action current line of the inferior laryngeal nerve showed regular oscillations having the same frequency as the voice line and changing with the pitch of the voice. Additional experiments led the author to assume that potential changes travel from the central organ to the larynx, although he does not feel justified in considering these regular action-potentials as originating in the higher centers of coördination. Records taken from the superior laryngeal nerve indicated that this nerve is largely sensory. Believing that a proprioceptive mechanism is responsible for the regular oscillation observed in the laryngeal nerve, the author states that further research will be necessary to study the suggested proprioceptive control of the action of the vocal cords.

RADIOLOGY

UNDER THE CHARGE OF
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The Abscess of Pott's Disease.—GHORMLEY (*Am. J. Roent. and Rad. Therap.*, 1929, **22**, 510) notes that the thoracic abscess of Pott's disease as seen with the Roentgen ray is of three types—the fusiform, the pyramidal and the globular. From a prognostic standpoint the globular type foretells a better course than the others. The pyramidal and fusiform varieties represent more extensive dissection beyond the original focus. Calcification of the contents of these abscesses occurs frequent and may appear as flocculent or flaky areas in the shadow or the entire shadow becomes dense; the calcification is of favorable significance, but cannot be regarded as an indication of complete healing. It is well known that fewer vertebræ are involved by about one-half in the average case of lumbar Pott's disease as compared with the thoracic variety. Any enlargement of the normal psoas shadow or along it, accompanying a spinal lesion, is presumptive evidence of tuberculosis of the spine with psoas abscess. Subsequently the abscess may absorb and leave little or no evidence of its former existence. Or it may calcify and enlarge or diminish, usually the latter if calcification is marked; ultimately calcified abscesses may reach a state where they no longer enlarge or decrease in size and may be regarded as dormant or silent. With the escape of a lumbar abscess to the subcutaneous tissue and drainage either spontaneously or by surgery, Roentgen ray evidence usually disappears. The most serious menace to life is the lumbar abscess; its effect on the deformity is of minor importance. On the other hand, the thoracic abscess is of less danger to life but a serious menace because of its effect on the deformity.

Bronchial Obstruction: Its Relation to Atelectasis, Bronchopneumonia and Lobar Pneumonia.—From the experimental and clinical investigations of atelectasis, postoperative pneumonitis and lobar pneumonia, CORYLLOS and BIRNBAUM (*Am. J. Roent. and Rad. Therap.*, 1929, **22**, 401) conclude that they are all produced by the same mechanism, bronchial obstruction. Any interference with the free drainage of the bronchial tree will cause lesions, the nature, extent, importance and evolution of which will depend on the degree and duration of the obstruction and nature and virulence of the microbes present. The identity in pathogenesis of these conditions is proved by the gross and microscopic appearances, their bacteriology, their circulatory disturbances, their evolution and the modifications in the pulmonary gaseous exchanges occurring in them. Between them there are, in degree only, differences in local and general symptoms, roentgenographic signs and

bronchoscopic findings. The rational treatment of these conditions should be based on their etiology and, as in every other obstructive lesion, should aim to relieve the obstruction and reëstablish free drainage in the bronchial tree. Lobar pneumonia is a pneumococcic bronchial obstruction with a combined atelectasis and pneumococcic cellulitis of the corresponding pulmonary area. Treatment should be directed not only against the bacteriemia, but chiefly against the local or pulmonary lesion. Carbon dioxid inhalation in 5 to 10 per cent concentration seems to possess a specific action against pneumococcic pulmonary infections, and, according to experimental and clinical data, could be used both as a preventive and curative agent.

Roentgen Therapy in Acute Inflammatory Conditions.—Roentgen treatment of acute inflammatory conditions is of great help to surgery and also to more conservative methods, in the opinion of MAY (*Radiology*, 1930, **14**, 411). It cannot replace old methods, but it is a very helpful adjunct to them. It not only alleviates pain, but also affects the entire process of inflammation. It should not be undertaken without proper surgical supervision. Its beneficial action is both local and general. The local effects are hyperemia, dilatation of the blood-vessels, increased circulation of the lymph and other local immunizing processes. In general, it tends to increase the specific and nonspecific forces of resistance. The optional dose of radiation lies between 130 and 300 *R* units on the skin over the inflamed area, using heavy filtration and high voltage. Two hundred and thirty-five cases, comprising furuncle, osteomyelitis, paronychia, pneumonia and various other acute inflammations, were subjected to Roentgen treatment by the author, and definite benefit resulted in 81.3 per cent.

Roentgenologic Diagnosis of Diseases of the Upper Respiratory Tract in Children.—PANCOAST and PENDERGRASS (*Am. J. Roent. and Rad. Therap.*, 1930, **23**, 241) hold that roentgenologic studies of the chests of infants and young children should always include the neck in order to detect possible obstructive lesions in the upper repiratory tract that may explain, wholly or in part, suspected intrathoracic conditions. The posterior border of the tongue, uvula, pharyngeal cavity and its walls, epiglottis, aryepiglottic folds, pyriform sinuses, laryngeal vestibuli, ventricular and vocal folds, and laryngeal ventricles, are easily seen in roentgenograms of the neck. Among the pathologic conditions amenable to roentgenologic diagnosis are: postdiphtheritic laryngeal stenosis, tuberculous adenitis with calcifications, retropharyngeal and retrotracheal abscess, encroachments on the nasopharynx, foreign bodies and the abnormal thymus. The stand is taken that thymic death is due largely to tracheostenosis, but is usually assisted by other factors causing upper respiratory obstruction. It is realized that much of the diagnosis of enlarged thymus is based on inadequate examination. The only definite or reliable signs of an enlarged or potentially obstructive thymus are narrowing of the trachea at the upper thoracic outlet on inspiration, too great a collapse on expiration or buckling at either phase, as shown by the lateral view, or lateral deviation of the trachea in the sagittal view. The thymus may be blamed for obstructive phenomena for which it is not responsible, and the examiner must have in

mind foreign bodies, retropharyngeal abscess, tracheal or laryngeal stenosis, recurrent laryngeal paralysis from the thymus, relaxed soft tissues of the pharynx and larynx in the young, asthma, whooping cough, meningitis and congenital cardiac conditions.

Changes Occurring in the Blood of the Newborn Following Ultraviolet Therapy.—In 50 newborn infants short exposure to the ultraviolet light increased the bleeding time and the blood platelets, according to SANFORD (*Arch. Phys. Therap., X-ray and Rad.*, 1930, **11**, 101). There was no effect on the coagulation time. Short exposures to the ultraviolet light would, therefore, serve as a therapeutic measure in infants with delayed bleeding time, but their coagulation time would have to be increased by other means. Short exposure of 200 newborn infants to ultraviolet light increased the hemoglobin content and number of red cells to a slight extent in an average number of cases. In cases in which the hemoglobin content and number of red cells are lower than normal the hemoglobin and cells are increased to a greater extent, and tend to remain nearly normal. Exposure of 120 newborn infants to ultraviolet light increased the total white count to a slight extent, the lymphocytes being increased at the expense of the polymorphonuclear leukocytes. The number of young or single-lobed nucleated cells of the polymorphonuclear cells were increased. The older or multilobed forms were decreased. There was a rapid return to normal.

Radiant Energy as Applied to Skin Lesions.—In the view of HIGHMAN (*Arch. Phys. Therap., X-ray and Rad.*, 1930, **11**, 123), a discussion of radiant energy in the treatment of skin lesions resolves itself into a comparison of the Roentgen ray with other forms of therapy. Destructive measures are superior to the Roentgen ray for neoplasms. Nothing equals the Roentgen ray, however, in treating the lymphatic infiltrations of the skin and in acne, with this reservation, that failure in so treating acne is encountered and that the lymphatic infiltrations sooner or later become unresponsive to any treatment, for they are fatal diseases. In part, the Grenz ray functions ambiguously in treating skin lesions. Radium is generally inferior to the Roentgen ray so far as skin lesions are concerned. The ultraviolet ray seems to have limited utility. Leaving out angioma serpiginosum, which is rare, and alopecia areata, in which it has some value, the ultraviolet ray does nothing that cannot be as well or better done in some other way. It does not compare with the Roentgen ray in acne or psoriasis, and has no value in the infections or neoplasms, save the Finsen ray, which stands out in the treatment of lupus vulgaris. Besides the diseases mentioned, epithelioma, particularly the basal-cell type, sarcoma of Kaposi, other sarcomata, the lymphodermas, mycosis, psoriasis, lichen planus and other scaling dermatoses are all amenable to the Roentgen ray. The infections more or less amenable to this ray are sarcoid and granuloma annulare, lupus vulgaris, rhinoscleroma, actinomycosis, perhaps blastomycosis, furunculosis and some forms of tinea. An unexplained phenomenon is the antipruritic action of the ray in some cases of vulvar and anal itching. The Roentgen ray is also used to produce epilation in tinea of the scalp. Permanent alopecia, as for hirsuties, should not be attempted.

NEUROLOGY AND PSYCHIATRY

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The Relationship of the Psychiatric Clinic to the Juvenile Court.—PLANT (*Ment. Hyg.*, 1929, **13**, 708) reviews the history of psychiatric advice in court work, beginning with Dr. William Healy's efforts in the Chicago Juvenile Court and its gradual spread. He calls attention to the fact that the physician's point of view is that of the individual, whereas the court's point of view is that of the community or of society. For this reason he considers that the court and the psychiatrist must always be opposed to each other, and that this is a healthy condition. The aim of the court is to see that society is protected, and the aim of the psychiatrist is to see that the individual factors are fully presented to the court. He cites a number of cases to demonstrate that many of the more or less serious social problems express a conflict between the needs of the individual and the needs of society and that many of the problems arise directly because we do have normal people in a normal social environment. He believes that the court and the psychiatrist will mutually increase the difficulties of the other. "To the judge now, and for the future, belongs the social responsibility and final disposition of all the data. We have little patience with any notion that this work should be taken out of legal hands even in the Juvenile Court. Our progress must ever rest upon the solidarity of our social institutions. Tugging and straining at this leash is always individual initiative, growth and idiosyncrasy. In our total social structure that is a necessary element. To present its fullest claims before the court, the psychiatric clinic exists. Our recommendations assume for the moment the paramount interests of the child, as if the whole world were to be built about his needs. It is, and will be, for the Juvenile Court to take these recommendations for review and replacement in the light of the needs of the solidarity and progress of our social institutions."

Predictability in the Administration of Criminal Justice.—GLUECK and GLUECK (*Ment. Hyg.*, 1929, **13**, 678) present a real contribution to criminologic research in this paper. The ideas in the article are taken from one chapter of the recently published book by the same authors, *Five Hundred Criminal Careers*. The authors call attention to the fact that the efforts to predict on the basis of statistical indices the recurrence of crime in individuals which have formerly been attempted have been subject to a number of faults which render them unreliable. They find that the usual reports of recurrence of criminality are far too low.

In their own study they found that only 20 per cent of the graduates of one of the better American reformatories have abandoned their lives of crime. To present sufficient data for an understanding of the tables and the method of derivation is beyond the scope of an abstract. The authors present evidence to show that the offense for which the person was sent to the reformatory has no bearing on the final outcome of the career. They offer four prognostic tables, the first of which is derived from an evaluation of the six most important pre-reformatory factors in the life of the criminal. They derive figures which should at least serve as an approximation of the probability of correction of criminality at the time that a judge is considering sentence to a reformatory. The second table is devised for use in considering parole from a reformatory and is based upon the six highest pre-reformatory factors and the highest reformatory factor (that is, that factor in the reformatory career which is most closely correlated with subsequent failure of parole). The next table is derived from the consideration of the pre-reformatory factors, the highest reformatory factor and the highest factor in parole life. It is designed for the determination of whether a criminal who has been on parole should be discharged or whether he should be continued under parole supervision. The fourth table adds to these former factors the five highest post-parole factors. It is easily seen that as new factors are added to the indices the degree of accuracy in predictability increases and this is exhibited by the actual facts of the tables. They present a sample of the application of this sort of prognostic procedure to actual criminal cases. The authors do not intend that these tables should be adopted immediately by the judiciary, but suggest some such prognostic method be worked out and tried out practically with a view to correcting its defects with the ultimate aim of attaining a prognostic instrument which could give a definite degree of probability in determining the disposition of criminal cases at any time that a change in the handling of that individual becomes necessary. In our opinion, the authors have made a distinct advance in this field.

Suggestions as to the Detection and Treatment of Personality Difficulties in College Students.—Estabrooks (*Ment. Hyg.*, 1929, **13**, 794) presents a development of mental hygiene at Colgate University, where they do not have a psychiatrist to carry on the work. This presentation must be of importance at the present time as the majority of our colleges and universities either do not have funds for psychiatric assistance in this work or are unable to obtain competent men to carry it on. The author calls attention to this and proceeds to tell us how the problem is handled at Colgate. All college freshmen are required to take the intelligence test for a college freshman as prepared by the American Council on Education. They fill out a vocational-interest blank and are given the Colgate tests for the detection of psychoneurotic traits and for introversion and extroversion. They have found that troubles of adjustment occur in the lower tenth of the intelligence scores and in the higher tenth of the psychoneurotic scores. The students in the first group (of low intelligence) are seen in the week after the opening of college. They are told frankly of their handicap, given some reassurance and encouraged to do their best. The group comprising the upper tenth in the psychoneurotic test are seen in the first or second

week of the term, usually under some fictitious reason. An attempt is made at this time to estimate the nervous stability of the student. From both of these groups those individuals who appear to be particularly susceptible to behavior disorders are selected out for further study. After these are disposed of, every member of the freshman class is interviewed for the purpose of vocational and educational guidance and at the same time a consideration is given to the mental hygiene viewpoint. While the majority of problems are revealed by these methods, some are overlooked. It is the practice at Colgate to confer with the teachers in rhetoric and debating, religion and ethics, because they have found a personality defect to show up quite frequently in these courses. Also use is made of faculty meetings where instructors are requested to report any queer students to the personnel department. Also a number of the freshman class who appear particularly stable are requested to keep an eye open for those students who are not making a good adjustment and to report them to the personnel department. The author recognizes the fact that a psychiatrist should be available for every problem case. "We should have a high grade psychiatrist on every problem case; only, in the first place, there are not enough Healys and Bronners to go around as has been pointed out before. Secondly, most institutions cannot afford such luxuries just at present. So we get on with what we have and pray for a better day to come." He points out that much can be done even in the absence of a psychiatrist.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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The Bacteriology of the Blood and Joints in Chronic Infectious Arthritis.—CECIL, NICHOLLS and STAINSBY (*Arch. Int. Med.*, 1929, **43**, 571) isolated a streptococcus from the circulating blood of patients with chronic infectious arthritis in 61.5 per cent of 78 cases. Of these streptococci, 83.3 per cent are culturally and biologically identical, and appear to be attenuated hemolytic streptococci. This dominant strain has been called the "typical strain." The remaining strains fall definitely into either the viridans or the indifferent group of streptococci. A streptococcus, culturally and biologically identical with the strain isolated from the blood, can sometimes be cultivated from one of the affected joints in the same patient. A streptococcus, culturally and biologically identical with the strain isolated from the blood and joints,

can sometimes be isolated from a focus of infection in the same patient. When the "typical strain" of streptococcus is injected intravenously into rabbits, a majority of the rabbits develop a chronic nonsuppurative polyarthritis. Microscopically, the histologic changes in the rabbit's joints are practically identical with those observed in the joints of patients with chronic infectious arthritis. Cultures from the blood and from the joints of rabbits infected with experimental arthritis frequently yield a streptococcus identical with the strain originally injected. These observations tend strongly to confirm the theory that chronic infectious arthritis is a streptococcal infection, caused in a large proportion of cases by a biologically specific strain of this organism. The presence of this specific strain of streptococcus in the blood of several patients with advanced arthritis deformans goes far to corroborate the view already widely held that arthritis deformans and chronic infectious arthritis are one and the same disease. The same authors studied the bacteriology of the blood and joints in rheumatic fever (*J. Exper. Med.*, 1929, **50**, 617). During the spring of 1928, 29 patients with acute rheumatic fever were subjected to blood cultures, of whom 9, or 31 per cent, yielded a streptococcus. During the spring of 1929, 31 patients with acute rheumatic fever were studied by blood cultures, of whom 26, or 83.9 per cent, yielded a streptococcus. The higher percentage of positive cultures in the 1929 series appears to have been due to improved cultural methods. Of the 35 strains of streptococci recovered from blood cultures, 33 have been classified as alpha streptococci (Streptococcus viridans); one as a beta streptococcus (Streptococcus hemolyticus); and one a gamma streptococcus (Streptococcus anhemolyticus). Some of the viridans strains produced very little green on blood media. Agglutination and absorption tests indicate that the strains of Streptococcus viridans recovered from the blood of patients with rheumatic fever show a tendency to fall into specific biologic groups. In 7 patients with rheumatic fever who were subjected to cultures from affected joints, 5, or 71.4 per cent, yielded a Streptococcus viridans. In 3 patients in whom green streptococci were recovered from both the blood and joint, agglutination and absorption tests proved the identity of the strains isolated from the two sources. These findings corroborate those of previous investigators and make it difficult to escape the conclusion that rheumatic fever is a streptococcal infection usually of the *alpha* or *viridans* type. The pathogenesis of rheumatic fever in respect to the joint lesions appears to be analogous to that of infectious arthritis and gonococcal arthritis. Bacterial allergy probably influences the clinical picture in all three conditions, but in each instance the joint manifestations are primarily dependent upon localization of bacteria in the joint, with subsequent infection.

Current Malaria Studies, with Special Reference to the Control Measures.—Williams (*Pub. Health Rep.*, 1929, **44**, 2001) notes that malaria has become more severe and has increased in amount in the southern states in the last few years, especially in 1927 and 1928. Some cases of the more severe forms of infection, hematuria, algid and cerebral, have occurred. Blood examinations have shown some very high rates, even up to 45 per cent. Most control work has been urban though rural infections have always been heavier. The cost of control

measures in rural areas is heavier than in urban. Quinin prophylaxis has not proven very effective but plasmochin is more promising and it is suggested that the inclusion of this drug in chill tonics would be advantageous. Screening is regarded as the sheet anchor of success and it can be carried out for as little as $8.00 per house. Another line of attack is in the use of Paris green as an anopheline larvacide.

Typhus Fever in the United States.—MAXCY (*Pub. Health Rep.*, 1929, **44**, 1735) presents a review of the subject, and the following discussion and summary: The evidence thus far adduced indicates that there is endemic in the United States a disease which is clinically indistinguishable from the mild typhus occurring during interepidemic periods in the Old World and in Mexico. The relationship of this disease to typhus is further borne out by serologic similarities. The Weil-Felix reaction is positive. The value of this observation in establishing the relationship of the disease in this country with that of the Old World has been modified by the recent discovery (Kerlee and Spencer), 1929 that the Weil-Felix reaction is positive in Rocky Mountain spotted fever, a disease which, though it belongs to the typhus group, is immunologically distinct. Observations in experimental animals are interpreted as meaning that the endemic typhus of the United States has common origin with the "tabardillo" of Mexico. The typhus which has been occurring in our eastern seaports does not depend upon direct importation from across the sea. It belongs to the North American Continent. In addition to the peculiarities of the virus, the disease in this country manifests certain epidemiologic characteristics which are in contrast with those generally attributed to the typhus of the Old World. They relate principally to the mode of transmission. These considerations have led to a tentative rejection of the human louse as the principal vector and of man as the principal reservoir of the disease in this part of the United States and the search for some other mode of transmission. In typhus fever it has been shown by Nicolle and others that beside the chimpanzee and the monkey certain small rodents are susceptible to the virus; that is, guinea pigs, rabbits, rats (white and gray), mice (white), and the gerbille. In a recent publication Nicolle (1926) reports a second series of passages of typhus virus through 12 generations of white rats. The question arises whether in the endemic typhus of the southeastern United States a reservoir of the disease may not exist other than in man, a rodent reservoir with accidental transmission to man through the bite of some parasitic bloodsucking insect or arachnid. Such a hypothesis is compatible with the epidemiologic characteristics which have been presented, namely: (1) The uneven focal distribution of the disease; (2) its sporadic occurrence; (3) its apparent lack of direct communicability from an infected person; (4) its association with the place of business rather than with the home, particularly with those premises upon which foodstuffs are handled or stored; (5) the recurrence of cases on the same premises after considerable intervals of time; (6) its seasonal incidence. Obviously, the rodents upon which suspicion immediately falls are rats and mice, and the parasitic intermediaries which are first suspected are fleas, mites, or possibly ticks. In summary, there is endemic in the United States a disease which resembles typhus and gives a positive Weil-Felix reaction. The virus of this disease has been identified with that of "tabardillo" in Mexico,

and both have been shown to be closely related to the virus of Old World typhus by immunologic tests. The North American strain appears to be originally derived from Old World sources. The epidemiology of the typhus of the United States is not compatible with man-to-man transmission by the louse. It suggests the existence of some other mechanism for the propagation of the virus. From a consideration of what is known of this group of diseases, the "rickettsias," and specifically with regard to the susceptibility of rodents to typhus virus, it seems probable that a reservoir may exist apart from man. A reservoir in rats or mice, with accidental transmission to man through the bite of some bloodsucking parasite, would be consistent with the known facts.

Septic Sore Throat.—Davis (*J. Am. Med. Assn.*, 1929, **93**, 978) claims that the present status of the epidemiology of septic sore throat is much the same as it was twenty years ago. Outbreaks are rare. They occur here and there and probably will continue to do so. No doubt, epidemics are now being observed that years ago would not have been recognized. Modern methods of pasteurization and the careful supervision of certified milk products, together with new methods of identifying Streptococcus epidemicus should do, and possibly have already done, much to prevent epidemics. Much still remains to be done, however, in the control of milk supplies before the disease can be completely eradicated.

PATHOLOGY AND BACTERIOLOGY

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Variation of Response to Infection with Treponema Pallidum Between an Albino and a Brown Breed of Rabbit.—The evidence presented by Frazier and Mu (*Proc. Soc. Exper. Biol. and Med.*, 1930, **27**, 243) indicated that albino rabbits were less resistant to infection with Treponema pallidum than were the brown breed. This was shown by extent and duration of the orchitis and the incidence of metastatic keratitis. The albino rabbits during the period of the most active clinical lesions were in poor general condition, being less active and showing changes in their hair, while the brown animals remained vigorous and well groomed.

The Local Effect of the Injection of Gases into the Subcutaneous Tissues.—The introduction of various gases into tissues and cavities has been carried out for many years in experimental studies, and in human cases for therapeutic purposes. The observations which were recorded in respect to these studies deal with the clinical signs, while none of them have indicated the reaction occurring in the tissues in

consequence to the presence of the foreign gas. However, Wolbach noted the tissue response arising through the presence of air in cases of interstitial emphysema associated with influenza. Recently, WRIGHT (*Am. J. Path.*, 1930, **6**, 87) studied the effect of a variety of gases when introduced into the tissues. He found that the subcutaneous injection of oxygen, nitrogen and carbon dioxid led to an inflammatory reaction with the presence of monocytes, epithelioid cells and giant cells, as seen in granulomata. The reactions are nonspecific, the monocytes, he believes, arise locally from some type of fixed connective-tissue cell, while the giant cells arise from the same source. Histologic studies resembling tubercles have been found quite commonly, and a fibrinous deposit is not infrequently seen within the gas spaces. These spaces become lined by mesothelial-like cells within six to eight days.

Lymphogranulomatosis of Lung.—WEBER (*Ziegler's Beit. f. Path. Anat.*, 1930, **84**, 1) discusses 7 cases of Hodgkin's disease which had involved lung. Three of these cases appeared to have their beginning in the lung structure, while 4 others were located within the thoracic glands and had secondarily invaded the lung. Only one of these cases was correctly diagnosed clinically, while one was diagnosed by microscopic sections during life. In the remaining group a diagnosis of tuberculosis was usually offered, and in one case was found at autopsy to be present along with the nodules of Hodgkin's disease. The granulomatous masses may be small and local, or may involve the whole lobe. Occasionally multiple, small nodules are scattered through several lobes. The process of necrosis may be more pronounced in Hodgkin's disease of the lung than is usually noted in the lymphatic glands. Cavities may be formed. The structure of the granulomatous mass simulates that encountered in other tissues. The author found that radiation inhibits somewhat the progress of the lesion. The granulomatous mass may give rise to small nodular processes in the intima of vessels. These nodules may develop to obstruct the lumen.

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